STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 149953

TO: Dwayne C Jones **Location: 3b87 / 3c70** **Wednesday, April 06, 2005** **Art Unit: 1614** **Phone: 571-272-0578** **Serial Number: 10 / 761096**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Remsen 1a51** **Phone: 571-272-22504** **jan.delaval@uspto.gov**

Search Notes

149953

Jones, Dwayne

From: Chan, Christina
Sent: Monday, April 04, 2005 6:08 PM
To: Jones, Dwayne; STIC-Biotech/ChemLib
Subject: RE: RUSH

Please rush. Thanks Chris

Chris Chan
TC 1600 New Hire Training Coordinator and SPE 1644
(571)-272-0841
Remsen, 3E89

-----Original Message-----
From: Jones, Dwayne
Sent: Monday, April 04, 2005 12:46 PM
To: Chan, Christina
Subject: FW: RUSH

Christina,

I believe that you can approve RUSH searches, if not sorry (who does?). Could you approve of this RUSH request for me please?

Dwayne

-----Original Message-----
From: Jones, Dwayne
Sent: Monday, April 04, 2005 12:43 PM
To: Richter, Johann
Subject: RUSH

Johann,

I have a late Reissue, 10/761,096, that needs an action by this Friday, could you pleas approve a RUSH for this appicaiton? Thanks in advance.

Dwayne

http://expoweb1:8001/cgi-bin/expo/GenInfo/pnquery.pl?PAT_ID=5336691

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Wednesday, April 06, 2005

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT; PLUR=YES; OP=OR		
☐	L7	L6 or l5	71
☐	L6	L4 and l1	31
☐	L5	$6tramadol near5 ((phenacetin or acetaminophen) or ($6acetamino near4 phenol))	53
☐	L4	L3 and l2	475
☐	L3	(phenacetin or acetaminophen) or ($6acetamino near4 phenol)	6655
☐	L2	$6tramadol	1035
☐	L1	(514/629,646,649,650)![CCLS]	2183

END OF SEARCH HISTORY

Rush

149953
Access DB# ____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Dwayne C. Jones Examiner #: 7099 Date: 05 APR 05
Art Unit: 1614 Phone Number 30 2-0578 Serial Number: 10/761,696
Mail Box and Bldg/Room Location: (3C70 and 3B37) REMSEN Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

***

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: see attached sheet

Inventors (please provide full names): ____

Earliest Priority Filing Date: ~~[illegible]~~ 06 SEP 91

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

1 — ~~Also please do a litigation search too.~~ [illegible] 4-5-05

2 — Please search claims 6 and 16

~~[illegible]~~

***

STAFF USE ONLY

Searcher: Jan	Type of Search		Vendors and cost where applicable	
Searcher Phone #: 22504	NA Sequence (#)		STN	✓
Searcher Location:	AA Sequence (#)		Dialog	
Date Searcher Picked Up 4/6/05	Structure (#)		Questel/Orbit	
Date Completed 4/6/05	Bibliographic	✓	Dr.Link	
Searcher Prep & Review Time	Litigation		Lexis/Nexis	
Clerical Prep Time: 15	Fulltext		Sequence Systems	
Online Time 40	Patent Family		WWW/Internet	
	Other		Other (specify)	

PTO-1590 (8-01)

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=> d his

     (FILE 'HOME' ENTERED AT 07:06:24 ON 06 APR 2005)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 07:06:33 ON 06 APR 2005
               E TRAMADOL/CN
L1           1 S E3
               E C16H25NO2/MF
L2         149 S E3 AND (46.150.18 AND 46.150.1)/RID
L3           4 S L2 AND TRAMADOL
L4          29 S L2 AND CYCLOHEXANOL AND DIMETHYLAMINO AND METHOXYPHENYL
L5          25 S L4 NOT L1,L3
L6          13 S L5 AND 3 METHOXYPHENYL
               SEL RN 4 5 13
L7           3 S E1-E3
L8           7 S L1,L3,L7
               SEL RN
L9          71 S E4-E10/CRN
               E ACETAMINOPHEN/CN
L10          1 S E3
L11        395 S C8H9NO2/MF AND 46.150.18/RID AND 1/NR
L12         66 S L11 AND HYDROXYPHENYL
L13         36 S L12 AND ACETAMIDE
L14         24 S L13 AND 4
L15          1 S L10 AND L14
               SEL RN
L16        325 S E1/CRN
L17          2 S L9 AND L16
L18         69 S L9 NOT L17
L19         43 S L18 AND (MXS/CI OR COMPD OR WITH)
L20         26 S L18 NOT L19
L21        301 S L16 AND (MXS/CI OR COMPD OR WITH)
L22          2 S L21 AND C16H25NO2
L23          2 S L17,L22
L24         24 S L16 NOT L21

     FILE 'HCAPLUS' ENTERED AT 07:23:11 ON 06 APR 2005
L25         15 S L23
L26          2 S L25 AND (RAFFA R? OR VAUGHT J?)/AU
L27          1 S L25 AND (ORTHO? OR MCNEIL? OR MC NEIL?)/PA,CS
L28          1 S L25 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L29          2 S L26-L28
L30       1058 S L8 OR L20
L31       1144 S TRAMADOL OR U26255A OR U()(26255A OR 26255 A OR 26 255A OR 26
L32         17 S 2 DIMETHYLAMINO METHYL 1 3 METHOXYPHENYL CYCLOHEXANOL
L33          1 S 2()(DIMETHYL OR DIMETHYL OR DI METHYL OR DIME)()AMINO METHYL
L34         45 S TRAMAL OR CG315 OR CG 315
L35       1198 S L30-L34
L36      11440 S L15 OR L24
L37       7018 S ACETAMINOPHEN? OR TYLENOL
L38         98 S (4 OR P OR PARA)()(HYDROXYPHENYL OR HYDROXY PHENYL)()ACETAMID
L39       4876 S PARACETAMOL
L40         15 S 4()(ACETYLAMINO OR ACETYL AMINO)()PHENOL
L41        463 S (4 OR P)()ACETAMIDOPHENOL
L42        404 S (4 OR P)()(HYDROXYACETANILIDE OR HYDROXY ACETANILIDE)
L43         63 S ABENSANIL OR ACAMOL OR ACENOL OR ACETAGESIC OR ACETALGIN OR A
L44        368 S CLARATAL OR CLIXODYNE OR CROCIN# OR DAFALGAN# OR DAPHALGAN# O
L45        175 S FEBROGESIC OR FEBRO GESIC OR FEBROLIN# OR FENDON# OR FEPANIL#
L46       4951 S NEBS OR NOBEDON# OR NSC109028 OR NSC()(109028 OR 109 028) OR
L47        990 S PARALEN# OR PARAMOL? OR PARASPEN# OR PARELAN# OR PARMOL OR PA
L48          8 S TABALGIN# OR TACHIPIRINA OR TAPAR OR TEMLO OR TEMPANAL OR TEM
L49         11 S ACETYL(1W)(HYDROXYANILINE OR HYDROXY ANILINE)
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L50          327 S ACETYLAMINOPHENOL OR ACETYL AMINOPHENOL OR ACETYL AMINO PHENO
L51         1563 S ACETANILIDE(L)HYDROXY
L52          372 S ACETYL(1W)(AMINOPHENOL OR AMINO PHENOL)
L53        16899 S L36-L52
L54          201 S L35 AND L53
L55            6 S L54 AND (RAFFA ? OR VAUGHT ?)/AU
L56            5 S L54 AND (ORTHO? OR MCNEIL? OR MC NEIL?)/PA,CS
L57            9 S L55,L56
L58            8 S L57 NOT PSOAS/TI
L59           12 S L54 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L60           10 S L59 NOT L29,L58
                 SEL DN AN 1 2
L61            2 S L60 AND E2-E7
L62           10 S L29,L58,L61
L63           10 S L62 AND L25-L62
L64            4 S L63 AND TRAMADOL(S)(HCL OR HYDROCHLORIDE)
L65           10 S L63,L64
                 SEL RN

     FILE 'REGISTRY' ENTERED AT 07:51:18 ON 06 APR 2005
L66          192 S E8-E199
L67            2 S L66 AND L23
L68            6 S L66 AND L8,L9
L69           17 S L66 AND L15,L16
L70           10 S L66 AND L24
L71            6 S L69 NOT L15,L70
L72            5 S L71 NOT 330988-71-1
L73           19 S L67,L68,L70,L72
L74          173 S L66 NOT L73
L75            8 S L74 AND (46.150.18 AND 46.150.1)/RID
                 SEL RN 2-6
L76            5 S E200-E204
L77           24 S L73,L76

     FILE 'HCAPLUS' ENTERED AT 07:57:05 ON 06 APR 2005
L78           10 S L77 AND L65
L79           94 S L76
L80         1124 S ?TRAMADOL?
L81          194 S L79,L80 AND L53
L82           10 S L81 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L83            6 S L82 NOT L78
L84           10 S L78 AND L25-L65,L78-L83
                 SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 07:58:51 ON 06 APR 2005
L85           25 S E205-E229

=> fil reg
FILE 'REGISTRY' ENTERED AT 07:59:12 ON 06 APR 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:     5 APR 2005  HIGHEST RN 847968-12-1
DICTIONARY FILE UPDATES:    5 APR 2005  HIGHEST RN 847968-12-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.
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**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information. *
*                                                                    *
**********************************************************************

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can tot l85

L85  ANSWER 1 OF 25  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   209967-51-1  REGISTRY
ED   Entered STN:  16 Aug 1998
CN   Acetamide, N-(4-hydroxyphenyl)-, magnesium salt (2:1) (9CI)  (CA INDEX
     NAME)
MF   C8 H9 N O2 . 1/2 Mg
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL
CRN  (103-90-2)
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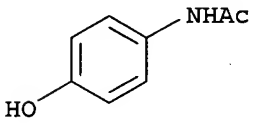

●1/2 Mg

Hit compounds for references 1-10 set L84, pages 30-68

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              4 REFERENCES IN FILE CA (1907 TO DATE)
              4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE   1:  135:14351

REFERENCE   2:  134:33001

REFERENCE   3:  132:54898

REFERENCE   4:  129:113538

L85  ANSWER 2 OF 25  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   209967-50-0  REGISTRY
ED   Entered STN:  16 Aug 1998
CN   Acetamide, N-(4-hydroxyphenyl)-, monocesium salt (9CI)  (CA INDEX NAME)
MF   C8 H9 N O2 . Cs
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL
CRN  (103-90-2)
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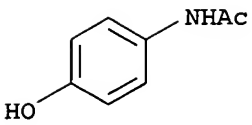


● Cs

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

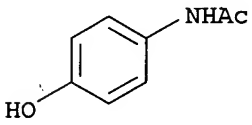
REFERENCE 1: 135:14351

REFERENCE 2: 134:33001

REFERENCE 3: 132:54898

REFERENCE 4: 129:113538

L85 ANSWER 3 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **209967-48-6** REGISTRY
ED Entered STN: 16 Aug 1998
CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt (9CI) (CA INDEX NAME)
MF C8 H9 N O2 . Li
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (103-90-2)



● Li

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

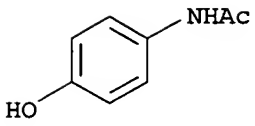
REFERENCE 1: 135:14351

REFERENCE 2: 134:33001

REFERENCE 3: 132:54898

REFERENCE 4: 129:113538

L85 ANSWER 4 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **209967-47-5** REGISTRY
ED Entered STN: 16 Aug 1998
CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1) (9CI) (CA INDEX NAME)
MF C8 H9 N O2 . 1/2 Ca
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (103-90-2)



●1/2 Ca

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

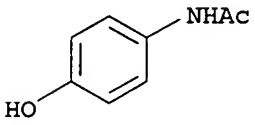
REFERENCE 1: 135:14351

REFERENCE 2: 134:33001

REFERENCE 3: 132:54898

REFERENCE 4: 129:113538

L85 ANSWER 5 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **209967-46-4** REGISTRY
ED Entered STN: 16 Aug 1998
CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt, hexahydrate (9CI) (CA INDEX NAME)
MF C8 H9 N O2 . 6 H2 O . Li
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (103-90-2)



● Li

●6 H_2O

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

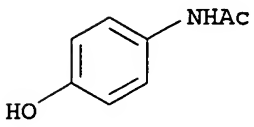
REFERENCE 1: 134:33001

REFERENCE 2: 132:54898

REFERENCE 3: 129:113538

L85 ANSWER 6 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **209967-45-3** REGISTRY
ED Entered STN: 16 Aug 1998

CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1), dihydrate (9CI) (CA INDEX NAME)
MF C8 H9 N O2 . 1/2 Ca . H2 O
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (103-90-2)



●1/2 Ca

● H_2O

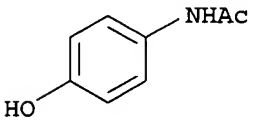
3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 134:33001

REFERENCE 2: 132:54898

REFERENCE 3: 129:113538

L85 ANSWER 7 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **209967-44-2** REGISTRY
ED Entered STN: 16 Aug 1998
CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt, heptahydrate (9CI) (CA INDEX NAME)
MF C8 H9 N O2 . 7 H2 O . Na
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (103-90-2)



● Na

●7 H_2O

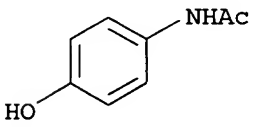
3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 134:33001

REFERENCE 2: 132:54898

REFERENCE 3: 129:113538

L85 ANSWER 8 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **209967-42-0** REGISTRY
ED Entered STN: 16 Aug 1998
CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt, hexahydrate (9CI) (CA INDEX NAME)
MF C8 H9 N O2 . 6 H2 O . Na
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (103-90-2)



● Na

●6 H_2O

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

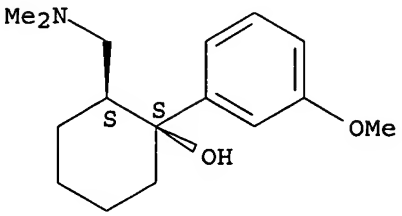
REFERENCE 1: 134:33001

REFERENCE 2: 132:54898

REFERENCE 3: 129:113538

L85 ANSWER 9 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **148229-79-2** REGISTRY
ED Entered STN: 22 Jun 1993
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1S,2S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1S-cis)-
OTHER NAMES:
CN (-)-(1S,2S)-Tramadol hydrochloride
CN (-)-Tramadol
CN E 381
FS STEREOSEARCH
DR 194224-67-4
MF C16 H25 N O2 . Cl H
CI COM
SR CA
LC STN Files: ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CHEMCATS, CIN, EMBASE, MEDLINE, PROMT, SYNTHLINE, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
CRN (123134-25-8)

Absolute stereochemistry. Rotation (-).



● HCl

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

46 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
46 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:190982

REFERENCE 2: 141:401084

REFERENCE 3: 141:130

REFERENCE 4: 140:399213

REFERENCE 5: 139:191276

REFERENCE 6: 139:143236

REFERENCE 7: 139:106588

REFERENCE 8: 138:100762

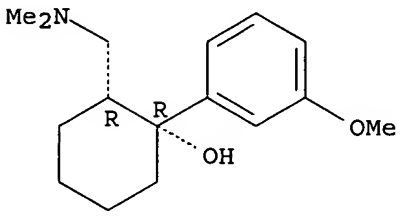
REFERENCE 9: 137:288205

REFERENCE 10: 136:299735

L85 ANSWER 10 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **148229-78-1** REGISTRY
ED Entered STN: 22 Jun 1993
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R-cis)-
OTHER NAMES:
CN (+)-Tramadol
CN (+)-trans-Tramadol hydrochloride
CN E 382
FS STEREOSEARCH
MF C16 H25 N O2 . Cl H
CI COM
SR CA
LC STN Files: ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS,

CASREACT, CHEMCATS, EMBASE, MEDLINE, PROMT, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
CRN (123154-38-1)

Absolute stereochemistry. Rotation (+).



● HCl

48 REFERENCES IN FILE CA (1907 TO DATE)
48 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:190982

REFERENCE 2: 141:401084

REFERENCE 3: 141:130

REFERENCE 4: 140:399213

REFERENCE 5: 140:368032

REFERENCE 6: 139:159829

REFERENCE 7: 139:143236

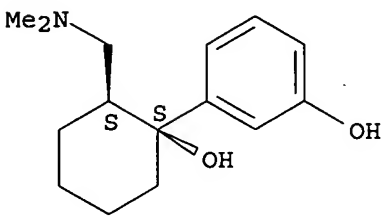
REFERENCE 8: 139:106588

REFERENCE 9: 138:100762

REFERENCE 10: 137:190754

L85 ANSWER 11 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **148218-19-3** REGISTRY
ED Entered STN: 22 Jun 1993
CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, hydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, hydrochloride, (1S-cis)-
OTHER NAMES:
CN (-)-O-Desmethyltramadol hydrochloride
CN EM 724
FS STEREOSEARCH
MF C15 H23 N O2 . Cl H
SR CA
LC STN Files: CA, CAPLUS, CHEMCATS, USPAT2, USPATFULL
CRN (144830-15-9)

Absolute stereochemistry. Rotation (-).



● HCl

10 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:36331

REFERENCE 2: 131:67592

REFERENCE 3: 127:292994

REFERENCE 4: 127:190519

REFERENCE 5: 126:171384

REFERENCE 6: 126:84457

REFERENCE 7: 126:69971

REFERENCE 8: 121:212995

REFERENCE 9: 119:80214

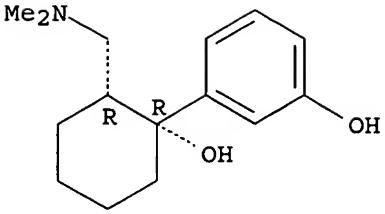
REFERENCE 10: 119:20350

L85 ANSWER 12 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **147731-80-4** REGISTRY
ED Entered STN: 25 May 1993
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with (1R-cis)-3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]phenol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, (1R-cis)-, mixt. contg. (9CI)
FS STEREOSEARCH
MF C15 H23 N O2 . C8 H9 N O2
CI MXS
SR CA
LC STN Files: CA, CAPLUS

CM 1

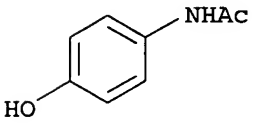
CRN 144830-14-8
CMF C15 H23 N O2

Absolute stereochemistry. Rotation (+).



CM 2

CRN 103-90-2
CMF C8 H9 N O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

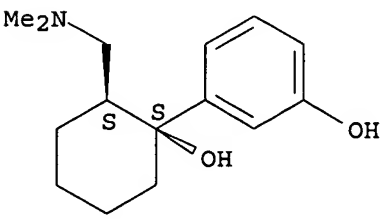
REFERENCE 1: 118:261016

L85 ANSWER 13 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **147731-79-1** REGISTRY
ED Entered STN: 25 May 1993
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with (1S-cis)-3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]phenol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, (1S-cis)-, mixt. contg. (9CI)
FS STEREOSEARCH
MF C15 H23 N O2 . C8 H9 N O2
CI MXS
SR CA
LC STN Files: CA, CAPLUS

CM 1

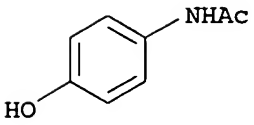
CRN 144830-15-9
CMF C15 H23 N O2

Absolute stereochemistry. Rotation (-).



CM 2

CRN 103-90-2
CMF C8 H9 N O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

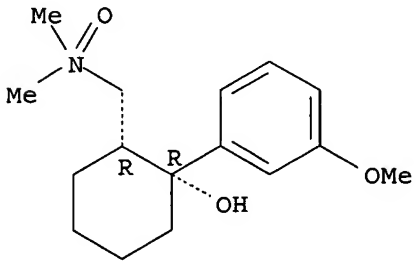
REFERENCE 1: 118:261016

L85 ANSWER 14 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **147657-25-8** REGISTRY
ED Entered STN: 20 May 1993
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-(±)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol N-oxide
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-(±)-2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)cyclohexanol
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, N-oxide, cis-(±)-, mixt. contg.
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, cis-(±)-, mixt. contg.
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, cis-, mixt. contg. (9CI)
FS STEREOSEARCH
MF C16 H25 N O3 . C8 H9 N O2
CI MXS
SR CA
LC STN Files: CA, CAPLUS

CM 1

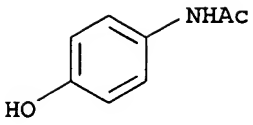
CRN 147441-56-3
CMF C16 H25 N O3

Relative stereochemistry.



CM 2

CRN 103-90-2
CMF C8 H9 N O2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

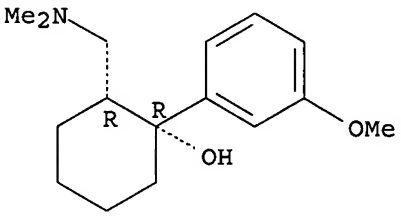
REFERENCE 1: 118:261016

L85 ANSWER 15 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **147630-10-2** REGISTRY
ED Entered STN: 19 May 1993
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-(±)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, cis-(±)-, mixt. contg.
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, cis-, mixt. contg. (9CI)
OTHER NAMES:
CN Acetaminophen-tramadol hydrochloride mixt.
FS STEREOSEARCH
MF C16 H25 N O2 . C8 H9 N O2 . Cl H
CI MXS
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 36282-47-0 (27203-92-5)
CMF C16 H25 N O2 . Cl H

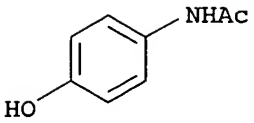
Relative stereochemistry.



● HCl

CM 2

CRN 103-90-2
CMF C8 H9 N O2



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 124:75606

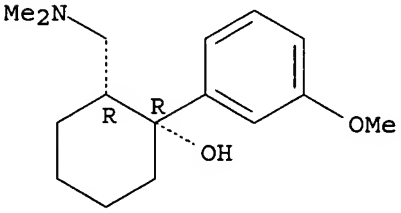
REFERENCE 2: 118:261016

L85 ANSWER 16 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **147630-09-9** REGISTRY
ED Entered STN: 19 May 1993
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with rel-(1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-(±)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-, mixt. contg. (9CI)
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, cis-(±)-, mixt. contg.
OTHER NAMES:
CN Acetaminophen-tramadol mixt.
CN Ultracet
FS STEREOSEARCH
MF C16 H25 N O2 . C8 H9 N O2
CI MXS
SR CA
LC STN Files: CA, CAPLUS, DIOGENES, TOXCENTER

CM 1

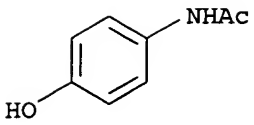
CRN 27203-92-5
CMF C16 H25 N O2

Relative stereochemistry.



CM 2

CRN 103-90-2
CMF C8 H9 N O2



13 REFERENCES IN FILE CA (1907 TO DATE)
14 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:254309

REFERENCE 2: 142:559

REFERENCE 3: 141:325105

REFERENCE 4: 141:128644

REFERENCE 5: 140:174755

REFERENCE 6: 139:317290

REFERENCE 7: 139:316390

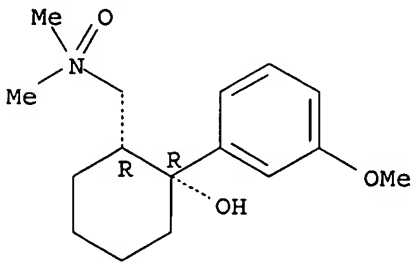
REFERENCE 8: 139:206925

REFERENCE 9: 139:111543

REFERENCE 10: 137:195456

L85 ANSWER 17 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **147441-56-3** REGISTRY
ED Entered STN: 07 May 1993
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, N-oxide, cis-(±)-
OTHER NAMES:
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, cis-
CN RWJ 38705
CN Tramadol N-oxide
FS STEREOSEARCH
MF C16 H25 N O3
CI COM
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, IPA, TOXCENTER, USPATFULL

Relative stereochemistry.



12 REFERENCES IN FILE CA (1907 TO DATE)
12 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:16861

REFERENCE 2: 140:228326

REFERENCE 3: 138:297047

REFERENCE 4: 138:66133

REFERENCE 5: 136:63545

REFERENCE 6: 134:202706

REFERENCE 7: 133:26418

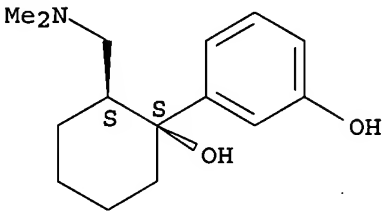
REFERENCE 8: 125:265758

REFERENCE 9: 121:212995

REFERENCE 10: 120:261350

L85 ANSWER 18 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **144830-15-9** REGISTRY
ED Entered STN: 10 Dec 1992
CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, (1S-cis)-
OTHER NAMES:
CN (-)-O-Demethyltramadol
CN (-)-O-Desmethyltramadol
FS STEREOSEARCH
MF C15 H23 N O2
CI COM
SR CA
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CHEMCATS, CSCHEM, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

24 REFERENCES IN FILE CA (1907 TO DATE)
24 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:150445

REFERENCE 2: 140:399213

REFERENCE 3: 140:263685

REFERENCE 4: 139:143236

REFERENCE 5: 139:46340

REFERENCE 6: 139:36331

REFERENCE 7: 138:82891

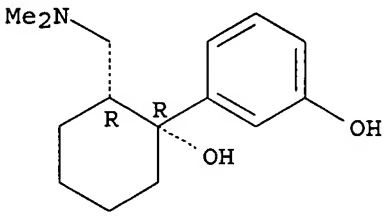
REFERENCE 8: 136:318793

REFERENCE 9: 135:146704

REFERENCE 10: 134:348298

L85 ANSWER 19 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **144830-14-8** REGISTRY
ED Entered STN: 10 Dec 1992
CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, (1R-cis)-
OTHER NAMES:
CN (+)-O-Demethyltramadol
CN (+)-O-Desmethyltramadol
FS STEREOSEARCH
MF C15 H23 N O2
CI COM
SR CA
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

29 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
29 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:150445

REFERENCE 2: 140:399213

REFERENCE 3: 140:263685

REFERENCE 4: 139:159829

REFERENCE 5: 139:143236

REFERENCE 6: 139:46340

REFERENCE 7: 139:36331

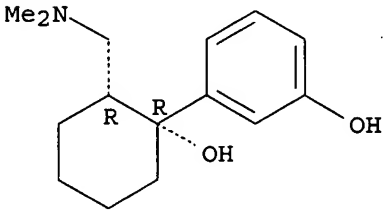
REFERENCE 8: 138:248554

REFERENCE 9: 138:82891

REFERENCE 10: 137:206539

L85 ANSWER 20 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **80456-81-1** REGISTRY
ED Entered STN: 16 Nov 1984
CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, rel-
(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, cis-(±)-
OTHER NAMES:
CN (RR,SS)-3-[2-[(Dimethylamino)methyl]-1-hydroxycyclohexyl]phenol
CN Mono-O-demethyltramadol
CN O-Demethyltramadol
CN O-Desmethyl tramadol
CN Phenol, 3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, cis-
FS STEREOSEARCH
DR 138853-72-2, 147859-77-6, 185502-38-9
MF C15 H23 N O2
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CHEMCATS, IPA, TOXCENTER,
USPAT2, USPATFULL
(*File contains numerically searchable property data)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

64 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
64 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:68465

REFERENCE 2: 142:32417

REFERENCE 3: 141:401084

REFERENCE 4: 141:337401

REFERENCE 5: 141:270940

REFERENCE 6: 141:230849

REFERENCE 7: 140:363057

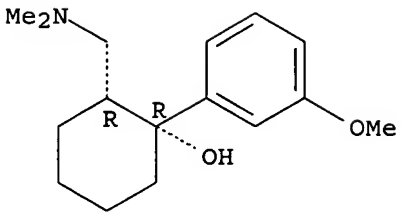
REFERENCE 8: 140:228837

REFERENCE 9: 140:228326

REFERENCE 10: 140:209862

L85 ANSWER 21 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **36282-47-0** REGISTRY
ED Entered STN: 16 Nov 1984
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, cis-(±)-
OTHER NAMES:
CN (±)-trans-2-[(Dimethylamino)methyl]-1-(m-methoxyphenyl)cyclohexanol hydrochloride
CN Adamon
CN Bellatram
CN CG 315
CN cis-Tramadol hydrochloride
CN Contramal
CN Crispin
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, cis-
CN Dolana
CN Mabron
CN Melanate
CN NIH 10969
CN Omnidol
CN Radol
CN Tadol
CN Topalgic
CN Trabar
CN Tradol
CN Tradol-Puren
CN Tradonal
CN Tramadex
CN Tramadol hydrochloride
CN Tramagetic
CN Tramagit
CN Tramal
CN Tramazac
CN Tramed
CN Tramol
CN Tridol
CN Ultram
CN Zumatran
CN Zydol
FS STEREOSEARCH
DR 53611-16-8, 22204-88-2, 194602-08-9
MF C16 H25 N O2 . Cl H
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES, EMBASE, HSDB*, IMSCOSEARCH, IPA, MEDLINE, MRCK*, PATDPASPC, PHAR, PROMT, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (27203-92-5)

Relative stereochemistry.



● HCl

257 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
259 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:246182

REFERENCE 2: 142:190907

REFERENCE 3: 142:168857

REFERENCE 4: 142:127290

REFERENCE 5: 142:127217

REFERENCE 6: 142:126508

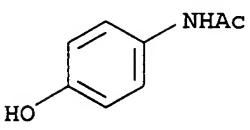
REFERENCE 7: 142:74343

REFERENCE 8: 142:48965

REFERENCE 9: 142:43799

REFERENCE 10: 142:43549

L85 ANSWER 22 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **35719-43-8** REGISTRY
ED Entered STN: 16 Nov 1984
CN Acetamide, N-(4-hydroxyphenyl)-, monopotassium salt (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetanilide, 4'-hydroxy-, monopotassium salt (8CI)
OTHER NAMES:
CN Potassium 4-(acetylamino)phenolate
CN Potassium 4-acetamidophenolate
MF C8 H9 N O2 . K
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
CRN (103-90-2)



● K

13 REFERENCES IN FILE CA (1907 TO DATE)
13 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:321237

REFERENCE 2: 137:353010

REFERENCE 3: 135:14351

REFERENCE 4: 134:33001

REFERENCE 5: 132:54898

REFERENCE 6: 129:113538

REFERENCE 7: 125:142293

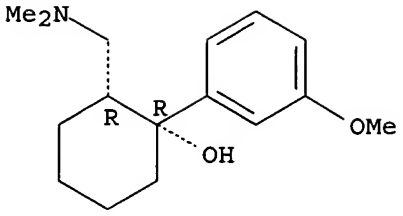
REFERENCE 8: 116:127907

REFERENCE 9: 105:42720

REFERENCE 10: 105:162

L85 ANSWER 23 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **27203-92-5** REGISTRY
ED Entered STN: 16 Nov 1984
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, cis-(±)-
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(m-methoxyphenyl)- (8CI)
OTHER NAMES:
CN (±)-Tramadol
CN CG 315E
CN cis-Tramadol
CN E 265
CN Racemic tramadol
CN Tramadol
CN U 26255A
FS STEREOSEARCH
DR 113683-92-4, 73806-46-9
MF C16 H25 N O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IMSCOSEARCH, IMSPATENTS, IPA, MEDLINE, MRCK*, PHAR, PROMT, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

855 REFERENCES IN FILE CA (1907 TO DATE)
28 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
860 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 142:273874

REFERENCE 2: 142:273362

REFERENCE 3: 142:273292

REFERENCE 4: 142:266935

REFERENCE 5: 142:266843

REFERENCE 6: 142:255934

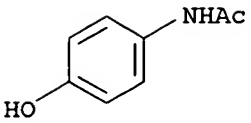
REFERENCE 7: 142:255929

REFERENCE 8: 142:253394

REFERENCE 9: 142:246187

REFERENCE 10: 142:246171

L85 ANSWER 24 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **16958-94-4** REGISTRY
ED Entered STN: 16 Nov 1984
CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 4'-Hydroxyacetanilide sodium salt
CN 4-Hydroxyacetanilide sodium salt
CN N-Acetyl-p-aminophenol sodium
CN Sodium 4-(acetylamino)phenolate
CN Sodium 4-acetamidophenoxide
CN Sodium p-acetamidophenolate
MF C8 H9 N O2 . Na
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMCATS, IFICDB, IFIPAT, IFIUDB, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
CRN (103-90-2)



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29 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
29 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 136:167774

REFERENCE 2: 135:14351

REFERENCE 3: 134:178922

REFERENCE 4: 134:33001

REFERENCE 5: 132:189291

REFERENCE 6: 132:54898

REFERENCE 7: 129:244813

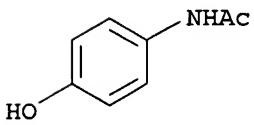
REFERENCE 8: 129:113538

REFERENCE 9: 128:145369

REFERENCE 10: 125:142293

L85 ANSWER 25 OF 25 REGISTRY COPYRIGHT 2005 ACS on STN
RN **103-90-2** REGISTRY
ED Entered STN: 16 Nov 1984
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Acetanilide, 4'-hydroxy- (7CI, 8CI)
OTHER NAMES:
CN 4'-Hydroxyacetanilide
CN 4-(Acetylamino)phenol
CN 4-(N-Acetylamino)phenol
CN 4-Acetamidophenol
CN 4-Acetaminophenol
CN 4-Hydroxyacetanilide
CN Abensanil
CN Acamol
CN Acenol
CN Acenol (pharmaceutical)
CN Acetagesic
CN Acetalgin
CN Acetaminofen
CN Acetaminophen
CN Algotropyl
CN Alpiny
CN Alvedon
CN Amadil
CN Anaflon
CN Anelix

CN Anhiba
CN Apamid
CN Apamide
CN APAP
CN Banesin
CN Ben-u-ron
CN Bickie-mol
CN Biocetamol
CN Calpol
CN Captin
CN Cetadol
CN Citramon P
CN Claratal
CN Clixodyne
CN Crocin
CN Dafalgan
CN Daphalgan
CN Datril
CN Dial-a-gesic
CN Dirox
CN Disprol
CN Doliprane
CN Dolprone
CN Duorol
CN Dymadon
CN Efferalgan
CN Endophy
CN Enelfa
CN Eneril
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS 3D CONCORD
DR 8055-08-1
MF C8 H9 N O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PATDPASPC, PHAR, PIRA, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11399 REFERENCES IN FILE CA (1907 TO DATE)
257 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
11421 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 142:285039

REFERENCE 2: 142:284995

REFERENCE 3: 142:284957

REFERENCE 4: 142:280793

REFERENCE 5: 142:279932

REFERENCE 6: 142:275180

REFERENCE 7: 142:274025

REFERENCE 8: 142:273807

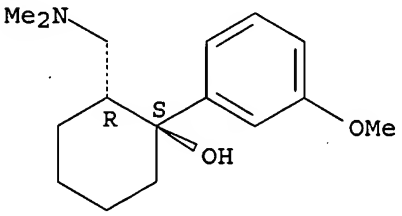
REFERENCE 9: 142:266797

REFERENCE 10: 142:266532

=> => d ide can tot

L86 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN **181289-59-8** REGISTRY
ED Entered STN: 26 Sep 1996
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1S,2R)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, trans-(-)-
FS STEREOSEARCH
MF C16 H25 N O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, CHEMCATS, CSCHEM, USPAT2, USPATFULL

Absolute stereochemistry. Rotation (-).



FYI only- used in search strategy

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7 REFERENCES IN FILE CA (1907 TO DATE)
7 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:263685

REFERENCE 2: 139:36331

REFERENCE 3: 137:288205

REFERENCE 4: 136:79238

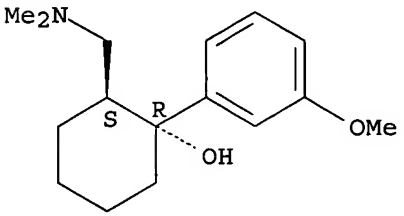
REFERENCE 5: 134:348187

REFERENCE 6: 132:298654

REFERENCE 7: 125:204663

L86 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN **181289-58-7** REGISTRY
ED Entered STN: 26 Sep 1996
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2S)-rel-(+)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, trans-(+)-
FS STEREOSEARCH
MF C16 H25 N O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, CHEMCATS, CSCHEM, USPAT2, USPATFULL

Rotation (+). Absolute stereochemistry unknown.



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7 REFERENCES IN FILE CA (1907 TO DATE)
7 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:74019

REFERENCE 2: 139:36331

REFERENCE 3: 137:288205

REFERENCE 4: 136:79238

REFERENCE 5: 134:348187

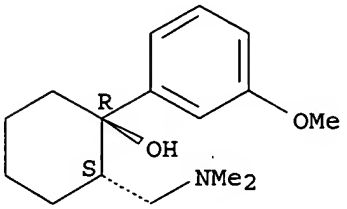
REFERENCE 6: 132:298654

REFERENCE 7: 125:204663

L86 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN 152538-36-8 REGISTRY
ED Entered STN: 27 Jan 1994
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2S)-rel-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, trans-
OTHER NAMES:
CN **(±)-trans-Tramadol**
CN **trans-Tramadol**
FS STEREOSEARCH
MF **C16 H25 N O2**
CI COM
SR CA
LC STN Files: ANABSTR, BIOSIS, CA, CAPLUS, CASREACT, TOXCENTER, USPAT2,

USPATFULL

Relative stereochemistry.



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26 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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REFERENCE 2: 141:355563

REFERENCE 3: 141:277348

REFERENCE 4: 139:276697

REFERENCE 5: 139:46340

REFERENCE 6: 139:36331

REFERENCE 7: 138:82891

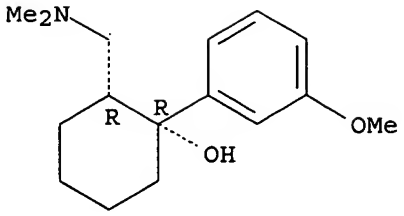
REFERENCE 8: 137:310691

REFERENCE 9: 137:288205

REFERENCE 10: 137:72521

L86 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN 123154-38-1 REGISTRY
ED Entered STN: 13 Oct 1989
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-
(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R-cis)-
OTHER NAMES:
CN **(+)-(R,R)-trans-Tramadol**
CN **(+)-trans-Tramadol free base**
FS STEREOSEARCH
DR 46941-74-6
MF **C16 H25 N O2**
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, RTECS*, TOXCENTER, USPAT2,
USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

27 REFERENCES IN FILE CA (1907 TO DATE)
27 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:150445

REFERENCE 2: 140:263685

REFERENCE 3: 139:369878

REFERENCE 4: 139:46340

REFERENCE 5: 139:36331

REFERENCE 6: 138:248554

REFERENCE 7: 137:288205

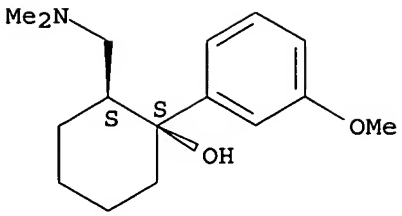
REFERENCE 8: 137:72521

REFERENCE 9: 136:318793

REFERENCE 10: 136:177417

L86 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN 123134-25-8 REGISTRY
ED Entered STN: 13 Oct 1989
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1S,2S)-
(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1S-cis)-
OTHER NAMES:
CN **(-)-(S,S)-trans-Tramadol**
FS STEREOSEARCH
DR 46941-76-8
MF **C16 H25 N O2**
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, RTECS*, TOXCENTER, USPAT2,
USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

24 REFERENCES IN FILE CA (1907 TO DATE)
24 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 141:150445

REFERENCE 2: 139:369878

REFERENCE 3: 139:46340

REFERENCE 4: 139:36331

REFERENCE 5: 137:288205

REFERENCE 6: 137:226635

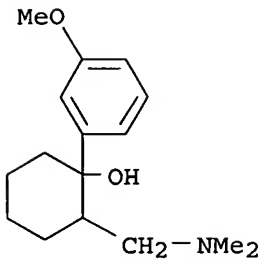
REFERENCE 7: 137:72521

REFERENCE 8: 136:318793

REFERENCE 9: 136:177417

REFERENCE 10: 135:357725

L86 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2005 ACS on STN
RN **2914-77-4** REGISTRY
ED Entered STN: 16 Nov 1984
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(m-methoxyphenyl)- (7CI)
OTHER NAMES:
CN 1-(m-Methoxyphenyl)-2-[(dimethylamino)methyl]cyclohexanol
CN 2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol
FS 3D CONCORD
MF C16 H25 N O2
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CHEMCATS, CHEMLIST, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

10 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 142:16861

REFERENCE 2: 139:276697

REFERENCE 3: 139:202672

REFERENCE 4: 134:56474

REFERENCE 5: 126:293443

REFERENCE 6: 82:21817

REFERENCE 7: 80:128176

REFERENCE 8: 80:128175

REFERENCE 9: 76:153321

REFERENCE 10: 63:54418

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 08:00:31 ON 06 APR 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 6 Apr 2005 VOL 142 ISS 15
FILE LAST UPDATED: 5 Apr 2005 (20050405/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d all hitstr tot l84

L84  ANSWER 1 OF 10  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2002:256052  HCAPLUS
DN   136:284456
ED   Entered STN:  05 Apr 2002
TI   Analgesic and glucosamine compositions
IN   Raffa, Robert; Cowan, Alan; Tallarida, Ronald
PA   Temple University, USA
SO   PCT Int. Appl., 24 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  A61K031-70
CC   63-6 (Pharmaceuticals)
FAN.CNT 1
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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PI   WO 2002026239         A1    20020404    WO 2001-US29606         20010921
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
             UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2423585             AA    20020404    CA 2001-2423585         20010921
     AU 2001092929          A5    20020408    AU 2001-92929           20010921
     EP 1328278             A1    20030723    EP 2001-973339          20010921
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
     US 2002058642          A1    20020516    US 2001-964178          20010925
PRAI US 2000-235405P        P     20000926
     WO 2001-US29606        W     20010921
CLASS
 PATENT NO.        CLASS   PATENT FAMILY CLASSIFICATION CODES
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 WO 2002026239     ICM     A61K031-70
 US 2002058642     ECLA    A61K031/00+A; A61K031/192; A61K031/70B+M
AB   This invention relates to a composition a glucosamine material and an analgesic
     compound such as a nonsteroidal anti-inflammatory drug (NSAID) and/or an
     opioid analgesic and its use for treatment of pain in pharmaceutical or
     veterinary applications.  When the components are administered within
     certain ratios, the analgesic efficacy of the composition is super-additive
     (synergistic) relative to the analgesic efficacy of the analgesic compound
     alone.  Solns. of glucosamine with ibuprofen or ketoprofen were given.
ST   analgesic NSAID glucosamine compn
IT   Analgesics
     Antiarthritics
     Antihistamines
     Bronchodilators
     Decongestants
     Muscle relaxants
        (analgesic and glucosamine compns.)
IT   Anti-inflammatory agents
        (nonsteroidal; analgesic and glucosamine compns.)
IT   Drug interactions
        (synergistic; analgesic and glucosamine compns.)
IT   66-84-2, Glucosamine hydrochloride 103-90-2,
     Acetaminophen  3416-24-8, Glucosamine  7512-17-6,
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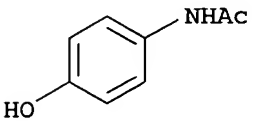
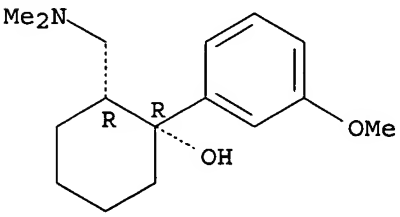
N-Acetylglucosamine 15307-86-5, Diclofenac 15687-27-1, Ibuprofen
22071-15-4, Ketoprofen **27203-92-5**, **Tramadol**
29031-19-4, Glucosamine sulfate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic and glucosamine compns.)
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Armitage; US 4501727 A 1985 HCAPLUS
IT **103-90-2**, **Acetaminophen 27203-92-5**,
Tramadol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic and glucosamine compns.)
RN 103-90-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-
(9CI) (CA INDEX NAME)

Relative stereochemistry.



L84 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:833143** HCAPLUS
DN **135:362611**
ED Entered STN: 16 Nov 2001
TI Opioid antagonist compositions and dosage forms
IN Sherman, Barry; Remien, Mary; Barbier, Remi; McGinity, James W.
PA Pain Therapeutics, Inc., USA; Albert Einstein College of Medicine of
Yeshiva University
SO PCT Int. Appl., 116 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61P
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001085257	A2	20011115	WO 2001-US14377	20010504
	WO 2001085257	A3	20020613		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,

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            RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
            VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
            DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
            BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
    US 6011004          A    20000104   US 1996-768221        19961217 <--
    AU 9947399          A1   19991028   AU 1999-47399         19990906
    WO 2000067739       A2   20001116   WO 2000-US12493       20000505
    WO 2000067739       A3   20010125
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    AU 2001059458       A5   20011120   AU 2001-59458         20010504
    EP 1284736          A2   20030226   EP 2001-932983        20010504
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    JP 2004515455       T2   20040527   JP 2001-581910        20010504
PRAI US 2000-202227P    P    20000505
    US 2000-202268P     P    20000505
    US 2000-566071      A    20000505
    WO 2000-US12493     W    20000505
    US 2000-244482P     P    20001030
    US 2000-245110P     P    20001101
    US 2000-246235P     P    20001102
    US 2001-756331      A    20010108
    US 1990-612847      B1   19901113  <--
    US 1993-153796      A1   19931117
    AU 1995-32769       A3   19950718
    US 1999-306164      A2   19990506
    WO 2001-US14377     W    20010504
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
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 WO 2001085257    ICM    A61P
 US 6011004       ECLA   A61K038/18F+M                                  <--
 JP 2004515455    FTERM  4C076/AA36; 4C076/AA44; 4C076/AA53; 4C076/BB01;
                         4C076/CC01; 4C076/CC04; 4C076/EE42H; 4C076/FF33;
                         4C084/AA17; 4C084/AA20; 4C084/AA23; 4C084/AA24;
                         4C084/MA02; 4C084/MA05; 4C084/MA35; 4C084/MA37;
                         4C084/MA52; 4C084/NA05; 4C084/NA11; 4C084/ZA082;
                         4C086/AA01; 4C086/AA02; 4C086/BC21; 4C086/CB23;
                         4C086/DA08; 4C086/MA01; 4C086/MA02; 4C086/NA05;
                         4C086/NA11; 4C086/ZA02; 4C086/ZA05; 4C086/ZA08;
                         4C086/ZB11; 4C206/AA01; 4C206/AA02; 4C206/FA10;
                         4C206/GA02; 4C206/GA31; 4C206/MA01; 4C206/MA02;
                         4C206/MA03; 4C206/MA04; 4C206/MA05; 4C206/MA55;
                         4C206/MA57; 4C206/MA72; 4C206/NA05; 4C206/NA06;
                         4C206/NA11; 4C206/ZA02; 4C206/ZA05; 4C206/ZA08;
                         4C206/ZB11
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AB The present invention is directed to novel dosage forms, pharmaceutical compns., kits, and methods of administration of an opioid antagonist at 0.0001-1.0 mg, including 0.0001-0.5 mg. Solid oral dosage forms are disclosed consisting essentially of an opioid antagonist or alternatively comprising an opioid antagonist and another active ingredient, such as an opioid agonist. Immediate release oral dosage forms are disclosed that release all or a substantial percentage of opioid antagonist, and another

active ingredient when present, in a desired time. Concurrent release dosage forms are disclosed that provide concurrent release of an opioid antagonist and another active ingredient. Thus, a suspension contained morphine sulfate (opioid agonist) 20, naltrexone (opioid antagonist) 0.05, talc 10, and Miglyol-812 qs to 100%.

ST opioid antagonist agonist pharmaceutical; morphine naltrexone pharmaceutical

IT Glycerides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10; opioid antagonist dosage forms)

IT Drug delivery systems
(beads; opioid antagonist dosage forms)

IT Drug delivery systems
(capsules; opioid antagonist dosage forms)

IT Drug delivery systems
(granules; opioid antagonist dosage forms)

IT Drug delivery systems
(immediate-release; opioid antagonist dosage forms)

IT Anti-inflammatory agents
(nonsteroidal; opioid antagonist dosage forms)

IT Analgesics
Anti-inflammatory agents
Containers
Dissolution rate
Opioid antagonists
Plasticizers
(opioid antagonist dosage forms)

IT Opioids
Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid antagonist dosage forms)

IT Drug delivery systems
(pellets; opioid antagonist dosage forms)

IT Drug delivery systems
(solids, oral; opioid antagonist dosage forms)

IT Drug delivery systems
(tablets; opioid antagonist dosage forms)

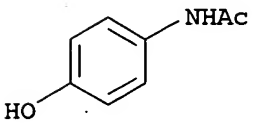
IT 329900-75-6, COX 2 329967-85-3, COX-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; opioid antagonist dosage forms)

IT 9004-34-6, Cellulose, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(microcryst.; opioid antagonist dosage forms)

IT 57-27-2, Morphine, biological studies 57-42-1, Meperidine 57-50-1, Sucrose, biological studies 63-42-3, Lactose 64-31-3, Morphine sulfate 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone **103-90-2**, **Acetaminophen** 124-90-3, Oxycodone hydrochloride 125-29-1, Hydrocodone 143-71-5, Hydrocodone bitartrate 437-38-7, Fentanyl 465-65-6, Naloxone 466-99-9, Hydromorphone 469-62-5, Propoxyphene 557-04-0 7757-93-9, Dibasic calcium phosphate 7789-77-7, Emcompress 9004-64-2, Hydroxypropyl cellulose 9004-65-3, HPMC 14807-96-6, Talc, biological studies 16590-41-3, Naltrexone 16676-29-2, Naltrexone hydrochloride 25322-68-3, Polyethylene glycol **27203-92-5**, **Tramadol** **36282-47-0**, **Tramadol hydrochloride** 55096-26-9, Nalmefene 71195-58-9, Alfentanil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid antagonist dosage forms)

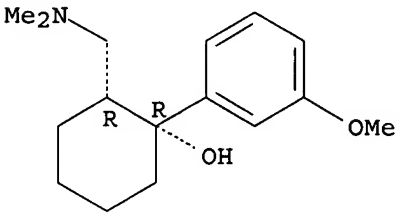
IT **103-90-2**, **Acetaminophen** **27203-92-5**, **Tramadol** **36282-47-0**, **Tramadol hydrochloride**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid antagonist dosage forms)

RN 103-90-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



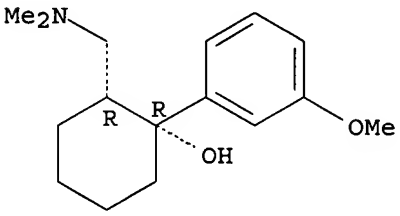
RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 36282-47-0 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

L84 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:833071** HCAPLUS
DN **135:352822**
ED Entered STN: 16 Nov 2001
TI Opioid agonist and antagonist compositions and methods for enhancing potency or reducing adverse side effects of opioid agonists
IN Sherman, Barry; Remien, Mary; Barbier, Remi; Dumas, Kathleen; Schoenhard, Grant
PA Pain Therapeutics, Inc., USA; Albert Einstein College of Medicine of Yeshiva University
SO PCT Int. Appl., 835 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 1-11 (Pharmacology)

Section cross-reference(s): 63

FAN.CNT 13

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001085150	A2	20011115	WO 2001-US14644	20010504
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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	AU 9947399	A1	19991028	AU 1999-47399	19990906
	WO 2000067739	A2	20001116	WO 2000-US12493	20000505
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	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2408098	AA	20011115	CA 2001-2408098	20010504
	EP 1280529	A2	20030205	EP 2001-933110	20010504
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	JP 2004501094	T2	20040115	JP 2001-581804	20010504
PRAI	US 2000-202227P	P	20000505		
	US 2000-202268P	P	20000505		
	US 2000-566071	A	20000505		
	WO 2000-US12493	W	20000505		
	US 2000-244482P	P	20001030		
	US 2000-245110P	P	20001101		
	US 2000-246235P	P	20001102		
	US 2001-756331	A	20010108		
	US 1990-612847	B1	19901113 <--		
	US 1993-153796	A1	19931117		
	AU 1995-32769	A3	19950718		
	US 1999-306164	A2	19990506		
	WO 2001-US14644	W	20010504		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001085150	ICM	A61K031-00
US 6011004	ECLA	A61K038/18F+M <--
JP 2004501094	FTERM	4C086/AA01; 4C086/AA02; 4C086/CB23; 4C086/MA02; 4C086/MA04; 4C086/MA05; 4C086/MA52; 4C086/MA56; 4C086/MA63; 4C086/MA66; 4C086/NA05; 4C086/NA06; 4C086/ZA08; 4C086/ZC02; 4C086/ZC75; 4C206/AA01; 4C206/AA02; 4C206/GA02; 4C206/GA31; 4C206/KA01; 4C206/MA02; 4C206/MA04; 4C206/MA05; 4C206/MA72; 4C206/MA76; 4C206/MA83; 4C206/MA86; 4C206/NA05; 4C206/NA06; 4C206/ZA08; 4C206/ZC02; 4C206/ZC75

AB The invention provides compns. and methods using an opioid agonist and an opioid antagonist to differentially dose a human subject so as to either enhance analgesic potency without attenuating an adverse side effect of the agonist, or alternatively maintain the analgesic potency of the

agonist while attenuating an adverse side effect of the agonist. The invention addnl. relates to novel opioid compns. and methods for the gender-based dosing of men and women.

ST adverse effect opioid agonist antagonist dosing; gender dosing opioid agonist antagonist; opioid agonist antagonist dosing analgesia

IT Puerperium
(and perinatal conditions; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Disease, animal
(asthenia; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Inflammation
(cellulitis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Eye, disease
(conjunctivitis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Intestine, disease
(constipation; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Biliary tract
Cardiovascular system
Connective tissue
Digestive tract
Ear
Joint, anatomical
Mammary gland
Nervous system
Prostate gland
Skeleton
Urinary tract
(disease; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Sleep
Vision
(disorder; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Toxicity
(drug; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Breathing (animal)
(dyspnea; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Urinary tract
(dysuria; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Nose
(epistaxis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Emotion
(euphoria; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Skin
(flush; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Mental disorder
(hallucinations; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Urine
(hematuria; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Reflex

(hiccup; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Muscle, disease
(hypertonia; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Tooth
(infection; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Drug delivery systems
(injections, i.m.; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Drug delivery systems
(injections, i.v.; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Drug delivery systems
(injections, s.c.; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Taste
(loss; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Headache
(migraine; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Drug delivery systems
(mucosal; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Muscle, disease
(myalgia; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Pharynx
(nasopharynx, nasopharyngitis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Adenoma
Analgesics
Anxiety
Blood pressure
Blood vessel, disease
Body temperature
Bone, disease
Calculi, biliary
Cough
Dermatitis
Diarrhea
Dizziness
Drug delivery systems
Drug interactions
Dysmenorrhea
Dyspepsia
Erythema
Eye, disease
Fatigue, biological
Fever and Hyperthermia
Flatulence
Headache
Hearing
Heart rate
Hemorrhage
Hypertension
Hypotension

Hypothermia
Infection
Injury
Kidney, disease
Mental disorder
Miosis
Muscle, disease
Nausea
Neoplasm
Opioid antagonists
Pain
Poisoning, biological
Pregnancy
Pruritus
Reproductive tract
Respiratory tract
Sex
Skin, disease
Sweat
Testis, disease
Tremor
Urogenital tract
Urticaria
Vasodilation
Vomiting
(opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Opioids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Mouth
(oral pain; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Drug delivery systems
(oral; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Abdomen
(pain; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Pharynx
(pharyngitis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Skin, disease
(photosensitivity; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Skin, disease
(rash; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Nose
(rhinitis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Mental activity
(sedation; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

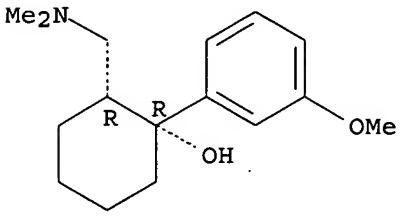
IT Organ, animal
(sensory; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)

IT Tremor
(shivering; opioid agonist and antagonist compns. and methods for

enhancing potency or reducing adverse side effects of opioid agonists)
IT Eyestalk
(sinus gland, congestion; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Muscle, disease
(spasm; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Mouth
(stomatitis; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Drug delivery systems
(sublingual; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Brain, disease
(syncope; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Heart, disease
(tachycardia; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Ear
(tinnitus; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Drug delivery systems
(transdermal; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Muscle
(twitch; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Respiratory tract
(upper, infection; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Urine
(urinary retention; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Mouth
(xerostomia; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT Opioid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(μ-opioid; opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT 57-27-2, Morphine, biological studies 64-31-3, Morphine sulfate 76-42-6, Oxycodone 125-29-1, Hydrocodone **27203-92-5**, **Tramadol 36282-47-0**, **Tramadol hydrochloride** 330988-71-1, Hydrocet
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT **103-90-2**, **Acetaminophen** 465-65-6, Naloxone 16590-41-3, Naltrexone 16676-29-2, Naltrexone hydrochloride 55096-26-9, Nalmefene
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
IT **27203-92-5**, **Tramadol 36282-47-0**,

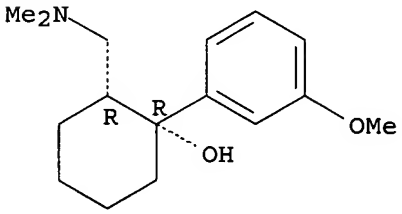
Tramadol hydrochloride
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



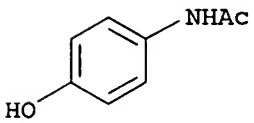
RN 36282-47-0 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

IT **103-90-2, Acetaminophen**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid agonist and antagonist compns. and methods for enhancing potency or reducing adverse side effects of opioid agonists)
RN 103-90-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:732199 HCAPLUS
DN 136:31212
ED Entered STN: 08 Oct 2001

TI Pharmacology of oral combination analgesics: Rational therapy for pain
AU **Raffa, R. B.**
CS Temple University School of Pharmacy, Philadelphia, PA, 19140, USA
SO Journal of Clinical Pharmacy and Therapeutics (2001), 26(4), 257-264
CODEN: JCPTED; ISSN: 0269-4727
PB Blackwell Science Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review.s. No single analgesic agent is perfect and no single analgesic can treat all types of pain. Yet each agent has distinct advantages and disadvantages compared to the others. Hence, clin. outcomes might be improved under certain conditions with the use of a combination of analgesics, rather than reliance on a single agent. A combination is most effective when the individual agents act through different analgesic mechanisms and act synergistically. By activating multiple pain-inhibitory pathways, combination analgesics can provide more effective pain relief for a broader spectrum of pain, and might also reduce adverse drug reactions. This overview highlights the therapeutic potential of combining analgesic medications with different mechanisms of action, particularly a nonsteroidal anti-inflammatory drug (NSAID) or **acetaminophen** with an opioid or **tramadol.**
ST review NSAID **acetaminophen** opioid **tramadol** analgesic combination pain
IT Anti-inflammatory agents
(nonsteroidal; pharmacol. of oral combination analgesics for pain in humans)
IT Analgesics
Human
(pharmacol. of oral combination analgesics for pain in humans)
IT Opioids
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of oral combination analgesics for pain in humans)
IT Drug interactions
(synergistic; pharmacol. of oral combination analgesics for pain in humans)
IT **103-90-2, Acetaminophen 27203-92-5, Tramadol**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of oral combination analgesics for pain in humans)
RE.CNT 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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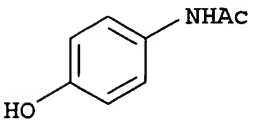
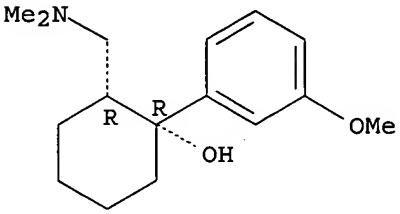
IT **103-90-2, Acetaminophen 27203-92-5, Tramadol**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of oral combination analgesics for pain in humans)
RN 103-90-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L84 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:875749 HCAPLUS
DN 134:33001
ED Entered STN: 14 Dec 2000
TI Alkali metal and alkaline-earth metal salts of **acetaminophen**
IN Ohannesian, Lena A.; Nadig, David; Higgins, John D., III; Rey, Max; Martellucci, Stephen A.
PA **McNeil-PPC, Inc., USA**
SO U.S., 10 pp., Cont.-in-part of U.S. Ser. No. 987,210, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-16
ICS C07C233-00
NCL 514629000
CC 63-6 (Pharmaceuticals)
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6160020	A	20001212	US 1998-100284	19980619
WO 9966919	A1	19991229	WO 1999-US13064	19990609

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,

ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9943380 A1 20000110 AU 1999-43380 19990609
PRAI US 1996-771176 B2 19961220
US 1997-987210 B2 19971209
US 1998-100284 A 19980619
WO 1999-US13064 W 19990609

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6160020	ICM	A61K031-16
	ICS	C07C233-00
	NCL	514629000
US 6160020	ECLA	A61K031/167; A61K045/06; C07C233/25
WO 9966919	ECLA	A61K031/167; A61K045/06

AB Isolated salts of **acetaminophen** are disclosed. Alkali metal and alkaline-earth metal salts of **acetaminophen** are formed by reacting the free acid of **acetaminophen** with the corresponding metal hydroxide and then immediately isolating the resulting salt. These salts have been found to be more water soluble and less bitter in taste than the free acid form of **acetaminophen.** The isolated salts may also be combined with other active ingredients. A tablet contained calcium **acetaminophen** 368.23, chlorpheniramine maleate 2, microcryst. cellulose 520.77, silica 4.5, and Mg stearate 4.5 mg.

ST **acetaminophen** metal salt prepn tablet; tablet calcium **acetaminophen** chlorpheniramine maleate

IT Drugs
(gastrointestinal; oral compns. containing **acetaminophen** metal salt and other actives)

IT Analgesics
Antihistamines
Antipyretics
Antitussives
Bronchodilators
Decongestants
Diuretics
Drug bioavailability
Expectorants
Hypnotics and Sedatives
(oral compns. containing **acetaminophen** metal salt and other actives)

IT Drug delivery systems
(oral; oral compns. containing **acetaminophen** metal salt and other actives)

IT Drug delivery systems
(tablets; oral compns. containing **acetaminophen** metal salt and other actives)

IT **209967-47-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oral compns. containing **acetaminophen** metal salt and other actives)

IT 50-78-2, Acetyl salicylic acid 51-43-4, Epinephrine 51-55-8, Atropine, biological studies 53-86-1, Indomethacin 58-08-2, Caffeine, biological studies 58-55-9, Theophylline, biological studies 58-73-1, Diphenhydramine 59-33-6, Pyrilamine 59-42-7, Phenylephrine 60-87-7, Promethazine 68-88-2, Hydroxyzine 73-31-4, Melatonin 76-42-6, Oxycodone 76-57-3, Codeine 77-09-8, Phenolphthalein 77-19-0, Dicyclomine 77-22-5, Caramiphen 77-23-6, Carbetapentane 86-22-6, Brompheniramine 90-82-4, Pseudoephedrine 91-81-6, Tripelennamine 93-14-1, Guaifenesin 104-31-4, Benzonatate; 113-92-8 125-29-1, Hydrocodone 125-71-3, Dextromethorphan 128-62-1, Noscapine 129-03-3,

Cyproheptadine 132-21-8, Dexbrompheniramine 299-42-3, Ephedrine; 317-34-0, Aminophylline 364-62-5, Metoclopramide 466-99-9, Hydromorphone 471-34-1, Calcium carbonate, biological studies 486-12-4, Triprolidine 554-10-9, 3-Iodo-1,2-propanediol 562-10-7, Doxylamine 586-06-1, Metaproterenol 606-04-2, Pamabrom. 616-91-1 642-72-8, Benzydamine 791-35-5, Chlophedianol 915-30-0, Diphenoxylate 2451-01-6, Terpin hydrate 3572-43-8, Bromhexine 3964-81-6, Azatadine 5104-49-4, Flurbiprofen 7020-55-5, Clidinium 7683-59-2, Isoprenaline 8050-81-5, Simethicone 12125-02-9, Ammonium chloride, biological studies 14838-15-4, Phenylpropanolamine 14882-18-9, Bismuth subsalicylate 15307-86-5, Diclofenac 15687-27-1, Ibuprofen **16958-94-4** 18053-31-1, Fominoben 18559-94-9, Albuterol; 18683-91-5, Ambroxol 21645-51-2, Aluminum hydroxide, biological studies 22071-15-4, Ketoprofen 22204-53-1, Naproxen 23031-25-6, Terbutaline 25523-97-1, Dexchlorpheniramine **27203-92-5**, **Tramadol** 29679-58-1, Fenoprofen 29975-16-4, Estazolam 30392-40-6, Bitolterol 33005-95-7, Tiaprofenic acid 34580-13-7, Ketotifen **35719-43-8** 36322-90-4, Piroxicam 36950-96-6, Cicloprofen 38194-50-2, Sulindac 41340-25-4, Etodolac 42924-53-8, Nabumetone 50679-08-8, Terfenadine 51481-61-9, Cimetidine 51803-78-2, Nimesulide 53179-11-6, Loperamide; 53716-49-7, Carprofen 54182-58-0, Sucralfate 57644-54-9, Bismuth subcitrate 61869-07-6, Domiodol 66357-35-5, Ranitidine 68844-77-9, Astemizole 71125-38-7, Meloxicam 73590-58-6, Omeprazole 74103-06-3, Ketorolac 74978-16-8, Magaldrate 75970-99-9, Norastemizole 76824-35-6, Famotidine 76963-41-2, Nizatidine 79794-75-5, Loratidine 80937-31-1, Flosulide 81098-60-4, Cisapride 82626-48-0, Zolpidem 83799-24-0, Fexofenadine; 83881-51-0, Cetirizine 86181-42-2, Temelastine 87848-99-5, Acrivastine 169590-42-5, Celecoxib 180200-68-4 **209967-48-6** **209967-50-0** **209967-51-1**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(oral compns. containing **acetaminophen** metal salt and other actives)

IT **209967-42-0P** **209967-44-2P** **209967-45-3P** **209967-46-4P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of **acetaminophen** metal salt to improve water solubility and taste)

IT **103-90-2**, **Acetaminophen** 1305-62-0, Calcium hydroxide, reactions 1310-65-2, Lithium hydroxide 1310-73-2, Sodium hydroxide, reactions 10043-52-4, Calcium chloride, reactions

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of **acetaminophen** metal salt to improve water solubility and taste)

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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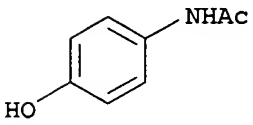
IT **209967-47-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oral compns. containing **acetaminophen** metal salt and other actives)

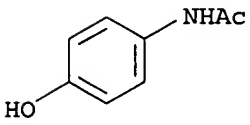
RN 209967-47-5 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1) (9CI) (CA INDEX NAME)



●1/2 Ca

IT **16958-94-4 27203-92-5, Tramadol**
35719-43-8 209967-48-6 209967-50-0
209967-51-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. containing **acetaminophen** metal salt and other actives)

RN 16958-94-4 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt (9CI) (CA INDEX NAME)

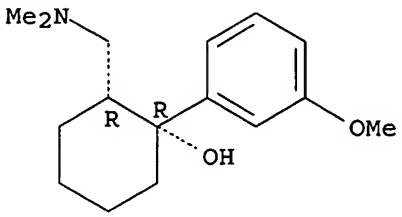


● Na

RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel-

(9CI) (CA INDEX NAME)

Relative stereochemistry.



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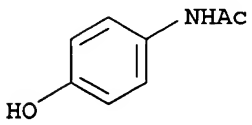
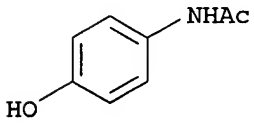


● K

RN 209967-48-6 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt (9CI) (CA INDEX NAME)



● Li

RN 209967-50-0 HCAPLUS
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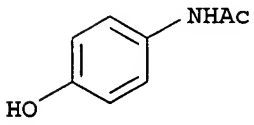

● Cs

RN 209967-51-1 HCAPLUS
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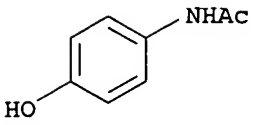
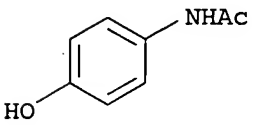


●1/2 Mg

IT **209967-42-0P 209967-44-2P 209967-45-3P**
209967-46-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **acetaminophen** metal salt to improve water solubility and taste)
RN 209967-42-0 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt, hexahydrate (9CI) (CA INDEX NAME)



● Na

●6 H_2O

RN 209967-44-2 HCAPLUS
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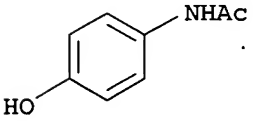
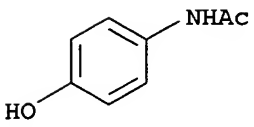


● Na

●7 H_2O

RN 209967-45-3 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1), dihydrate (9CI) (CA

INDEX NAME)



● 1/2 Ca

● H_2O

RN 209967-46-4 HCAPLUS
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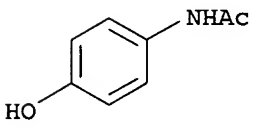
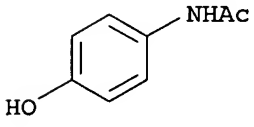


● Li

● 6 H_2O

IT **103-90-2, Acetaminophen**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **acetaminophen** metal salt to improve water solubility and taste)
RN 103-90-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



L84 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:819235 HCAPLUS
DN 132:54898
ED Entered STN: 30 Dec 1999
TI Pharmaceutical composition containing a salt of **acetaminophen** and at least one other active ingredient
IN Ohannesian, Lena A.; Nadig, David; Higgins, John D., III; Rey, Max; Martellucci, Stephen A.

PA **Mcneil-PPC, Inc., USA**
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-165
CC 63-6 (Pharmaceuticals)
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9966919	A1	19991229	WO 1999-US13064	19990609
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6160020	A	20001212	US 1998-100284	19980619
AU 9943380	A1	20000110	AU 1999-43380	19990609
PRAI US 1998-100284	A	19980619		
US 1996-771176	B2	19961220		
US 1997-987210	B2	19971209		
WO 1999-US13064	W	19990609		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9966919	ICM	A61K031-165
WO 9966919	ECLA	A61K031/167; A61K045/06
US 6160020	ECLA	A61K031/167; A61K045/06; C07C233/25

AB This invention relates to pharmaceutical compns. comprising an alkali or alkaline-earth metal salt of **acetaminophen** and at least one other active ingredient selected from the group consisting of analgesics, decongestants, expectorants, antitussives, antihistamines, gastrointestinal agents, diuretics, bronchodilators and mixts. thereof. The **acetaminophen** salts have both improved aqueous solubility and a less bitter taste than the free acid form of **acetaminophen.** A tablet contained **acetaminophen** calcium salt 368.23, chlorpheniramine maleate 2, microcryst. cellulose 520.77, Cab-O-Sil M5 4.5, and Mg stearate 4.5 mg.

ST tablet **acetaminophen** salt drug combination
IT Digestive tract
(disease, agents for; pharmaceutical compns. containing **acetaminophen** salts and other drugs)
IT Drug delivery systems
(oral; pharmaceutical compns. containing **acetaminophen** salts and other drugs)
IT Analgesics
Antihistamines
Antitussives
Bronchodilators
Decongestants
Diuretics
Drug bioavailability
Expectorants
(pharmaceutical compns. containing **acetaminophen** salts and other drugs)
IT Drug delivery systems
(tablets; pharmaceutical compns. containing **acetaminophen** salts and other drugs)
IT **209967-42-0P 209967-44-2P 209967-45-3P**
209967-46-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. containing **acetaminophen** salts and other drugs)

IT 50-78-2, Acetylsalicylic acid 51-43-4, Epinephrine 51-55-8, Atropine, biological studies 53-86-1, Indomethacin 58-08-2, Caffeine, biological studies 58-55-9, Theophylline, biological studies 58-73-1, Diphenhydramine 59-33-6, Pyrilamine 59-42-7, Phenylephrine 60-87-7, Promethazine 68-88-2, Hydroxyzine 73-31-4 76-42-6, Oxycodone 76-57-3, Codeine 77-09-8, Phenolphthalein 77-19-0, Dicyclomine 77-22-5, Caramiphen 77-23-6, Carbetapentane 86-22-6, Brompheniramine 90-82-4, Pseudoephedrine 91-81-6, Tripelennamine 93-14-1, Guaifenesin **103-90-2** 104-31-4, Benzonatate 113-92-8, Chlorpheniramine maleate 125-29-1, Hydrocodone 125-69-9, Dextromethorphan hydrobromide 125-71-3, Dextromethorphan 128-62-1, Noscapine 129-03-3, Cyproheptadine 132-21-8, Dexbrompheniramine 147-24-0, Diphenhydramine hydrochloride 299-42-3, Ephedrine 317-34-0, Aminophylline 345-78-8, Pseudoephedrine hydrochloride 364-62-5, Metoclopramide 466-99-9, Hydromorphone 471-34-1, Calcium carbonate, biological studies 486-12-4, Triprolidine 554-10-9, 3-Iodo-1,2-propanediol 562-10-7, Doxylamine 586-06-1, Metaproterenol 606-04-2, Pamabrom 616-91-1, N-Acetylcysteine 642-72-8, Benzydamine 791-35-5, Chlophedianol 915-30-0, Diphenoxylate 2451-01-6, Terpin hydrate 3572-43-8, Bromhexine 3964-81-6, Azatadine 5104-49-4, Flurbiprofen 7020-55-5, Clidinium 7683-59-2, Isoprenaline 8024-48-4, Casanthranol 8050-81-5, Simethicone 12125-02-9, Ammonium chloride, biological studies 14838-15-4, Phenylpropanolamine 14882-18-9, Bismuth subsalicylate 15307-86-5, Diclofenac 15687-27-1 **16958-94-4** 18053-31-1, Fominoben 18559-94-9, Albuterol 18683-91-5, Ambroxol 21645-51-2, Aluminum hydroxide (Al(OH)3), biological studies 22071-15-4, Ketoprofen 22204-53-1, Naproxen 23031-25-6, Terbutaline 25523-97-1, Dexchlorpheniramine **27203-92-5**, **Tramadol** 29679-58-1, Fenoprofen 29975-16-4, Estazolam 30392-40-6, Bitolterol 33005-95-7, Tiaprofenic acid 34580-13-7, Ketotifen **35719-43-8** 36322-90-4, Piroxicam 36950-96-6, Cicloprofen 38194-50-2, Sulindac 41340-25-4, Etodolac 42924-53-8, Nabumetone 50679-08-8, Terfenadine 51481-61-9, Cimetidine 51803-78-2 53179-11-6, Loperamide 53716-49-7, Carprofen 57644-54-9, Bismuth subcitrate 61869-07-6, Domiodol 66357-35-5, Ranitidine 68844-77-9, Astemizole 71125-38-7, Meloxicam 73590-58-6, Omeprazole 74103-06-3, Ketorolac 74978-16-8, Magaldrate 75970-99-9, Norastemizole 76824-35-6, Famotidine 76963-41-2, Nizatidine 79794-75-5, Loratidine 80937-31-1, Flosulide 82626-48-0, Zolpidem 83799-24-0, Fexofenadine 83881-51-0, Cetirizine 86181-42-2, Temelastine 87848-99-5, Acrivastine 169590-42-5, Celecoxib 180200-68-4 **209967-47-5** **209967-48-6** **209967-50-0** **209967-51-1**

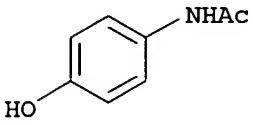
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing **acetaminophen** salts and other drugs)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Anon; 1996, 11, HCAPLUS
(2) Anon; 1997, V1997(07)
(3) Bottu; FR 2278324 A 1976 HCAPLUS
(4) Kiyotaka, O; US 5409709 A 1995 HCAPLUS
(5) Procter & Gamble; WO 9523595 A 1995 HCAPLUS
(6) Rama Rao India; IN 172949 A HCAPLUS
(7) SCR Newpharm; FR 2751875 A 1998 HCAPLUS
(8) Schering Corp; EP 0396404 A 1990 HCAPLUS
(9) Sunshine Abraham; WO 8504589 A 1985 HCAPLUS

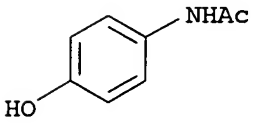
(10) Taisho Pharmaceut Co Ltd; JP 09-067256 A 1997 HCAPLUS
IT **209967-42-0P 209967-44-2P 209967-45-3P**
209967-46-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. containing **acetaminophen** salts and other drugs)
RN 209967-42-0 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt, hexahydrate (9CI) (CA INDEX NAME)



● Na

●6 H_2O

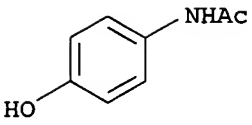
RN 209967-44-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt, heptahydrate (9CI) (CA INDEX NAME)



● Na

●7 H_2O

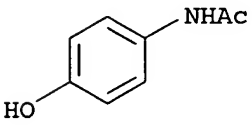
RN 209967-45-3 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1), dihydrate (9CI) (CA INDEX NAME)



●1/2 Ca

● H_2O

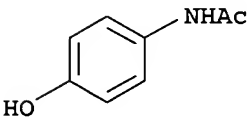
RN 209967-46-4 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt, hexahydrate (9CI) (CA INDEX NAME)



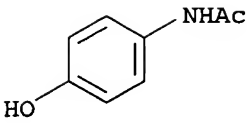
● Li

●6 H_2O

IT **103-90-2 16958-94-4 27203-92-5, Tramadol 35719-43-8 209967-47-5 209967-48-6 209967-50-0 209967-51-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing **acetaminophen** salts and other drugs)
RN 103-90-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



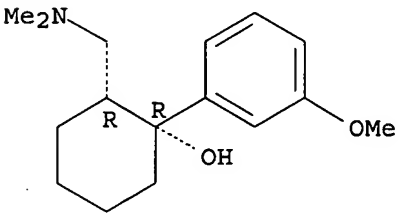
RN 16958-94-4 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monosodium salt (9CI) (CA INDEX NAME)



● Na

RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 35719-43-8 HCAPLUS
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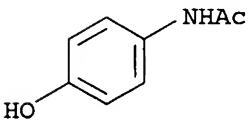
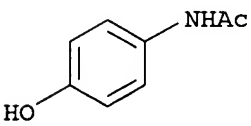


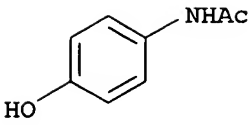
● K

RN 209967-47-5 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, calcium salt (2:1) (9CI) (CA INDEX NAME)



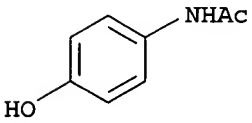
●1/2 Ca

RN 209967-48-6 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monolithium salt (9CI) (CA INDEX NAME)



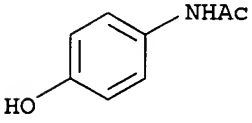
● Li

RN 209967-50-0 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, monocesium salt (9CI) (CA INDEX NAME)



● Cs

RN 209967-51-1 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, magnesium salt (2:1) (9CI) (CA INDEX NAME)



●1/2 Mg

L84 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:435283 HCAPLUS
DN 125:105766
ED Entered STN: 24 Jul 1996
TI Characterization of endothelin-induced nociception in mice: evidence for a mechanistically distinct analgesic model
AU **Raffa, Robert B.**; Schupsky, James J.; Lee, David K. H.; Jacoby, Henry I.
CS Drug Discovery, R. W. Johnson Pharm. Res. Inst., Spring House, PA, 19477-0776, USA
SO Journal of Pharmacology and Experimental Therapeutics (1996), 278(1), 1-7
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 1
AB The behavioral response elicited in mice by an i.p. injection of endothelin-1 (ET-1) (0.1 mg/kg) was differentiated from that elicited by

standard agents such as acetylcholine (ACh) (5.5 mg/kg) or phenyl-p-quinone (PpQ) (1.25 mg/kg). First, there was lack of two-way 'cross-tolerance' between test paradigms. I.e., at equieffective doses, a 60-min prior i.p. injection of ET-1 blocked the behavioral response to a subsequent i.p. injection of ET-1 or PpQ, but not of ACh, whereas a 60-min prior injection of ACh or of PpQ had no effect on a subsequent i.p. injection of ACh, PpQ or ET-1. Second, differential antagonism of ET-1-, ACh- or PpQ-induced responses was observed in an examination of 36 test compds. For example, cyclooxygenase inhibitors such as indomethacin and ibuprofen did not block the ET-1-induced response at >10 times the doses that blocked ACh- or PpQ-induced responses, whereas other compds. (such as certain benzodiazepines) inhibited ET-1-induced, but not ACh- or PpQ-induced, responses. These findings suggest that ET-1 produces a novel nociceptive stimulus, mechanistically distinct from ACh and PpQ. Hence, the ET-1-induced behavioral response in mice serves as a rapid and convenient measure of in vivo endothelin activity. In addition, this test might be a model for clin. pains not adequately treated by present analgesic agents or adequately tested by preclin. antinociceptive screens using ACh or PpQ. As such, it is a potentially valuable model for the identification of novel analgesic and other agents.

ST endothelin nociception analgesic screening

IT Analgesics
Drug tolerance
Pain
(endothelin-induced nociception in mice and mechanistically distinct analgesic and clin. pain model)

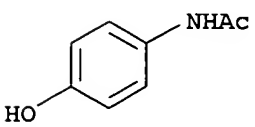
IT 50-06-6, Phenobarbital, biological studies 50-48-6, Amitriptyline 50-78-2, Aspirin 51-55-8, Atropine, biological studies 51-64-9, d-Amphetamine 52-53-9, Verapamil 53-86-1, Indomethacin 57-27-2, Morphine, biological studies 57-33-0 57-53-4, Meprobamate 58-25-3, Chlordiazepoxide 59-46-1, Procaine 68-88-2, Hydroxyzine 76-57-3, Codeine 92-13-7, Pilocarpine **103-90-2**, **Acetaminophen** 137-58-6, Lidocaine 359-83-1, Pentazocine 439-14-5, Diazepam 1134-47-0, Baclofen 1622-62-4, Flunitrazepam 4199-09-1, (-)Propranolol 4205-90-7, Clonidine 15687-27-1, Ibuprofen 17617-23-1, Flurazepam 22204-53-1, Naproxen **27203-92-5**, **Tramadol** 28911-01-5, Triazolam 28981-97-7, Alprazolam 35711-34-3, Tolmetin sodium 42399-41-7, Diltiazem 64603-91-4, THIP 78123-71-4, DAMGO 111406-87-2, Zileuton 132746-60-2, CP 96345
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic screening in endothelin-induced nociception mechanistically distinct model in mice)

IT 51-84-3, Acetylcholine, biological studies 106-51-4, p-Quinone, biological studies 123626-67-5, Endothelin-1
RL: ADV (Adverse effect, including toxicity); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(endothelin-induced nociception in mice and mechanistically distinct analgesic and clin. pain model)

IT **103-90-2**, **Acetaminophen** **27203-92-5**, **Tramadol**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic screening in endothelin-induced nociception mechanistically distinct model in mice)

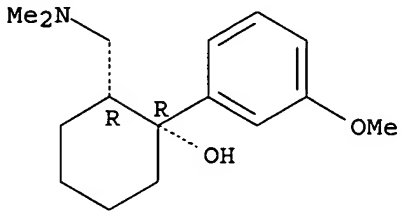
RN 103-90-2 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



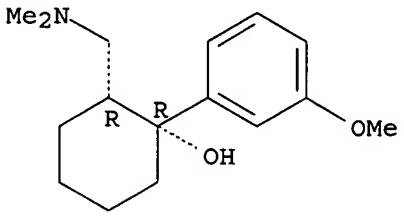
L84 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:992320 HCAPLUS
DN 124:75606
ED Entered STN: 20 Dec 1995
TI Testing for synergism over a range of fixed ratio drug combinations: replacing the isobologram.
AU Tallarida, Ronald J.; **Raffa, Robert B.**
CS Dep. Pharmacol., Temple Univ. Sch. Med., Philadelphia, PA, 19140-5104, USA
SO Life Sciences (1995), 58(2), PL23-PL28
CODEN: LIFSAK; ISSN: 0024-3205
PB Elsevier
DT Journal
LA English
CC 1-4 (Pharmacology)
AB An isobologram is a Cartesian plot of pairs of doses that, in combination, yield a specified level of effect. It is a convenient and presently popular way of graphically displaying results of drug-combination and similar studies, because paired values of exptl. points that fall below or above the line connecting the axial points (usually ED50 values) denote supra- and sub-additive combinations, resp. However, an isobologram does not fulfill the criteria for standard least squares regression anal. It is thus less useful for addressing questions related to the range of combination ratios over which synergy occurs. We describe a substitute for the isobologram, in which log(total-dose) is plotted against the proportion of a component in a combination. One advantage is that a nonlinear curve-fitting procedure and determination of the confidence interval of a single parameter allow the determination of departure from additivity over a range of fixed proportion mixts. An example is given of the combination of two analgesics (**acetaminophen** and **tramadol hydrochloride**). Another advantage of the new method is the reduction of animal use.
ST drug synergism math analysis
IT Pharmaceuticals
(testing for synergism over a range of fixed ratio drug combinations)
IT Statistics and Statistical analysis
(regression, testing for synergism over a range of fixed ratio drug combinations)
IT Drug interactions
(synergistic, testing for synergism over a range of fixed ratio drug combinations)
IT **147630-10-2, Acetaminophen-tramadol hydrochloride** mixture
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(testing for synergism over a range of fixed ratio drug combinations)
IT **147630-10-2, Acetaminophen-tramadol**

hydrochloride mixture
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(testing for synergism over a range of fixed ratio drug combinations)
RN 147630-10-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride (9CI) (CA INDEX NAME)

CM 1

CRN 36282-47-0
CMF C16 H25 N O2 . Cl H

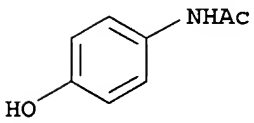
Relative stereochemistry.



● HCl

CM 2

CRN 103-90-2
CMF C8 H9 N O2



L84 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:612995 HCAPLUS
DN 121:212995
ED Entered STN: 29 Oct 1994
TI Composition comprising a **tramadol** material and **acetaminophen** and its use
IN **Raffa, Robert B.; Vaught, Jeffrey L.**
PA **McNeilab, Inc., USA**
SO U.S., 8 pp. Cont.-in-part of U.S. Ser. No. 755,924, abandoned.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-165
NCL 514629000
CC 63-6 (Pharmaceuticals)
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5336691	A	19940809	US 1992-974865	19921110 <--
	CA 2095523	AA	19930307	CA 1992-2095523	19920903 <--
	CA 2095523	C	20040622		

HU 64838	A2	19940328	HU 1993-1313	19920903	<--
HU 219332	B	20010328			
AT 169498	E	19980815	AT 1992-919762	19920903	<--
ES 2120451	T3	19981101	ES 1992-919762	19920903	<--
RU 2121346	C1	19981110	RU 1993-43625	19920903	<--
SG 80535	A1	20010522	SG 1996-5733	19920903	<--
ZA 9207434	A	19940328	ZA 1992-7434	19920928	<--
CN 1086133	A	19940504	CN 1992-112594	19921024	<--
CN 1071571	B	20010926			

PRAI US 1991-755924 B2 19910906 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5336691	ICM	A61K031-165
	NCL	514629000
US 5336691	ECLA	A61K031/165+M <--

AB This invention relates to a composition comprising **tramadol** or its various forms or salts and **acetaminophen**, and its use. The compns. are pharmacol. useful in treating pain and tissue conditions. The compns. are also subject to less opioid side-effects such a abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compns. are within certain ratios the pharmacol. effects of the compns. are superadditive (synergistic).

ST tranadol **acetaminophen** analgesic

IT Analgesics
Antihistaminics
Antitussives
Bronchodilators
Hypnotics and Sedatives
Muscle relaxants
(analgesic **acetaminophen-tramadol** compns.)

IT **144830-14-8P 144830-15-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(analgesic **acetaminophen-tramadol** compns.)

IT **103-90-2, Acetaminophen 27203-92-5, Tramadol 36282-47-0, Tramadol hydrochloride 147441-56-3, Tramadol** N-oxide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic **acetaminophen-tramadol** compns.)

IT **148229-78-1, (+)-Tramadol 148229-79-2, (-)-Tramadol**
RL: RCT (Reactant); RACT (Reactant or reagent)
(analgesic **acetaminophen-tramadol** compns.)

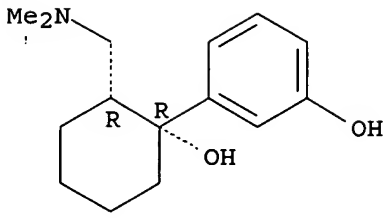
IT **148218-19-3P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(analgesic **acetaminophen-tramadol** compns.)

IT **144830-14-8P 144830-15-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(analgesic **acetaminophen-tramadol** compns.)

RN 144830-14-8 HCAPLUS

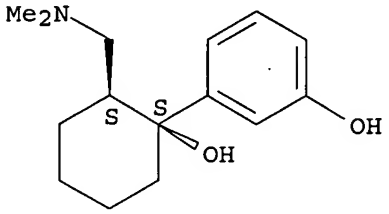
CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

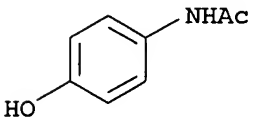


RN 144830-15-9 HCAPLUS
CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

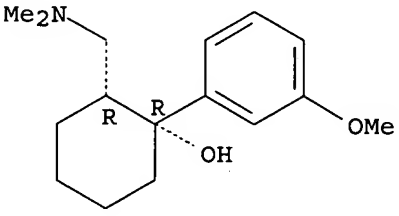


IT **103-90-2, Acetaminophen 27203-92-5, Tramadol 36282-47-0, Tramadol hydrochloride 147441-56-3, Tramadol** N-oxide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic **acetaminophen-tramadol** compns.)
RN 103-90-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



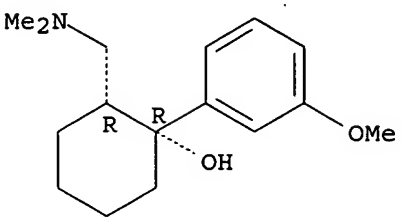
RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 36282-47-0 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

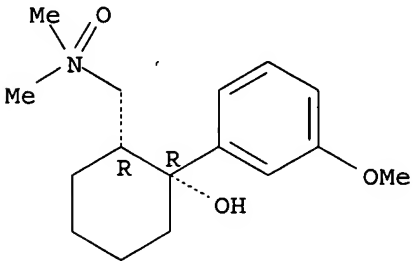
Relative stereochemistry.



● HCl

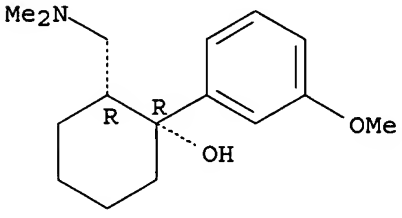
RN 147441-56-3 HCAPLUS
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **148229-78-1**, (+)-**Tramadol** **148229-79-2**, (-)-**Tramadol**
RL: RCT (Reactant); RACT (Reactant or reagent)
(analgesic **acetaminophen-tramadol** compns.)
RN 148229-78-1 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)- (9CI) (CA INDEX NAME)

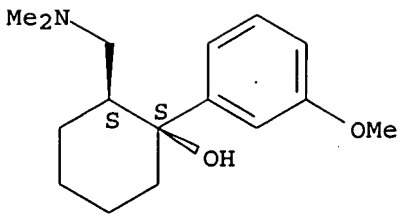
Absolute stereochemistry. Rotation (+).



● HCl

RN 148229-79-2 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1S,2S)- (9CI) (CA INDEX NAME)

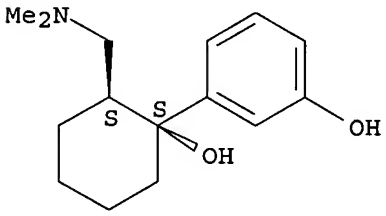
Absolute stereochemistry. Rotation (-).



● HCl

IT **148218-19-3P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(analgesic **acetaminophen-tramadol** compns.)
RN 148218-19-3 HCAPLUS
CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

L84 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:261016 HCAPLUS
DN 118:261016
ED Entered STN: 26 Jun 1993
TI Pharmaceutical composition comprising **tramadol** and **acetaminophen** for treatment of pain
IN **Raffa, Robert B.**
PA **McNeilab, Inc., USA**
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-16
ICS A61K031-13
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9304675	A1	19930318	WO 1992-US7542	19920903 <--

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RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG

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AU 651247	B2	19940714			
EP 566709	A1	19931027	EP 1992-919762	19920903	<--
EP 566709	B1	19980812			
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HU 219332	B	20010328			
JP 06502869	T2	19940331	JP 1993-505447	19920903	<--
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CN 1086133	A	19940504	CN 1992-112594	19921024	<--
CN 1071571	B	20010926			
PRAI US 1991-755924	A	19910906	<--		
WO 1992-US7542	A	19920903			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9304675	ICM	A61K031-16
	ICS	A61K031-13

AB Synergistic mixture of **tramadol** (I) and **acetaminophen** (II) are used for treatment of pain. The mixture has little opioid side-effects such as abuse, tolerance, constipation, and respiratory depression. A solution contained I 8, II 400 mg and water to 10 mL. The effects of the solution were studied in acetylcholine-induced abdominal constriction test in mice.

ST synergistic **tramadol acetaminophen** pharmaceutical pain

IT Analgesics
(**tramadol-acetaminophen** mixture, synergisticc)

IT **147630-09-9 147630-10-2 147657-25-8**
147731-79-1 147731-80-4
RL: BIOL (Biological study)
(pharmaceutical composition containing, for treatment of pain)

IT **27203-92-5P, Tramadol**
RL: PREP (Preparation)
(preparation of, for N-oxide derivative preparation)

IT **80456-81-1P**, O-Desmethyl **tramadol**
RL: PREP (Preparation)
(preparation of, for treatment of pain)

IT **147630-09-9 147630-10-2 147657-25-8**
147731-79-1 147731-80-4
RL: BIOL (Biological study)
(pharmaceutical composition containing, for treatment of pain)

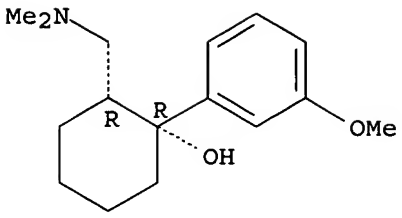
RN 147630-09-9 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with rel-(1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (9CI) (CA INDEX NAME)

CM 1

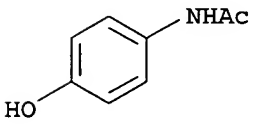
CRN 27203-92-5
CMF C16 H25 N O2

Relative stereochemistry.



CM 2

CRN 103-90-2
CMF C8 H9 N O2

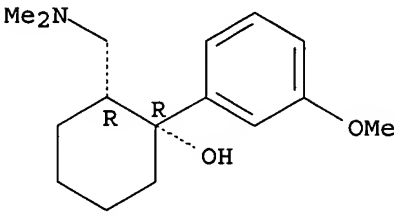


RN 147630-10-2 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride (9CI) (CA INDEX NAME)

CM 1

CRN 36282-47-0
CMF C16 H25 N O2 . Cl H

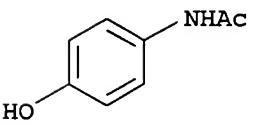
Relative stereochemistry.



● HCl

CM 2

CRN 103-90-2
CMF C8 H9 N O2



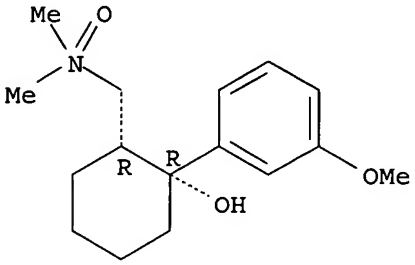
RN 147657-25-8 HCAPLUS

CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with cis-2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (9CI) (CA INDEX NAME)

CM 1

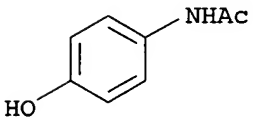
CRN 147441-56-3
CMF C16 H25 N O3

Relative stereochemistry.



CM 2

CRN 103-90-2
CMF C8 H9 N O2

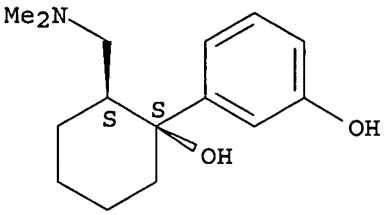


RN 147731-79-1 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with (1S-cis)-3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]phenol (9CI) (CA INDEX NAME)

CM 1

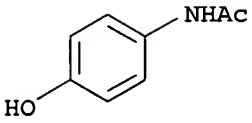
CRN 144830-15-9
CMF C15 H23 N O2

Absolute stereochemistry. Rotation (-).



CM 2

CRN 103-90-2
CMF C8 H9 N O2

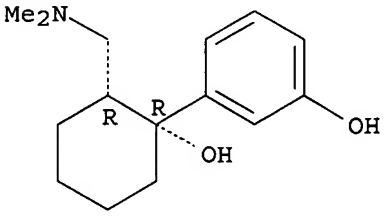


RN 147731-80-4 HCAPLUS
CN Acetamide, N-(4-hydroxyphenyl)-, mixt. with (1R-cis)-3-[2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]phenol (9CI) (CA INDEX NAME)

CM 1

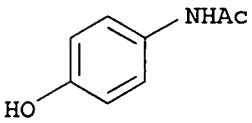
CRN 144830-14-8
CMF C15 H23 N O2

Absolute stereochemistry. Rotation (+).



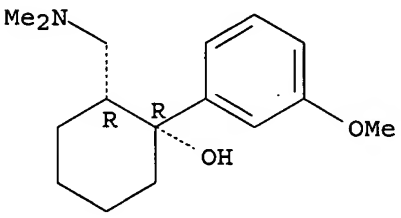
CM 2

CRN 103-90-2
CMF C8 H9 N O2



IT **27203-92-5P, Tramadol**
RL: PREP (Preparation)
(preparation of, for N-oxide derivative preparation)
RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

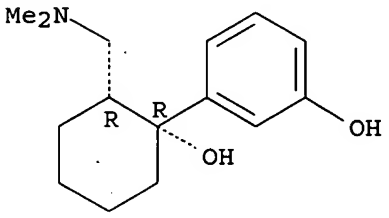
Relative stereochemistry.



IT **80456-81-1P**, O-Desmethyl **tramadol**
RL: PREP (Preparation)
(preparation of, for treatment of pain)
RN 80456-81-1 HCAPLUS

CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, rel-
(9CI) (CA INDEX NAME)

Relative stereochemistry.



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FOR DETAILS. <<<

=> d all abeq tech abex tot

L107 ANSWER 1 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2000-147173 [13] WPIX
DNC C2000-046031
TI Pharmaceutical composition comprising an isolated **acetaminophen**
salt and at least one other active agent, has improved analgesic ability.
DC B05
IN HIGGINS, J D; MARTELLUCCI, S A; NADIG, D; OHANNESIAN, L A; REY, M
PA (MCNI) **MCNEIL-PPC INC**
CYC 84
PI WO 9966919 A1 19991229 (200013)* EN 30 A61K031-165
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ UG ZW
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GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD
MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA

UG UZ VN YU ZA ZW
AU 9943380 A 20000110 (200025) A61K031-165
US 6160020 A 20001212 (200067) A61K031-16
ADT WO 9966919 A1 WO 1999-US13064 19990609; AU 9943380 A AU 1999-43380 19990609; US 6160020 A CIP of US 1996-771176 19961220, CIP of US 1997-987210 19971209, US 1998-100284 19980619
FDT AU 9943380 A Based on WO 9966919
PRAI US 1998-100284 19980619; US 1996-771176 19961220; US 1997-987210 19971209
IC ICM A61K031-16; A61K031-165
ICS C07C233-00
AB WO 9966919 A UPAB: 20000313
NOVELTY - Pharmaceutical composition comprising an isolated **acetaminophen** salt (I) and at least one other active agent selected from analgesics, decongestants, expectorants, antitussives, antihistamines, gastrointestinal agents, diuretics and/or bronchodilators, is new.

DETAILED DESCRIPTION - Pharmaceutical composition comprises an isolated **acetaminophen** salt of formula (I) and at least one other active agent selected from analgesics, decongestants, expectorants, antitussives, antihistamines, gastrointestinal agents, diuretics and/or bronchodilators.

n = 1 or 2;

M = alkali metal when n is 1 and M is alkaline earth metal when n is 2; and

x = 0-10.

ACTIVITY - Analgesic; antipyretic.

MECHANISM OF ACTION - None given.

USE - The composition is used to elicit onset of hastened analgesic or antipyretic response (claimed).

ADVANTAGE - (I) have significantly increased dissolution rates compared to the conventional free acid form of **acetaminophen.** (I) have improved taste compared to the conventional form of **acetaminophen.** The increased solubility results in faster peak **acetaminophen** plasma concentration which will potentially provide faster onset of action of the analgesic and/or antipyretic activity. In a test using 0.1 N HCl and a USP Dissolution Apparatus 2 (paddle speed: 50 rpm) at 37 deg. C, the concentration of **acetaminophen** at 30 s was 0.30 mg/ml for **acetaminophen** sodium salt, 0.32 mg/ml for **acetaminophen** lithium salt and 0.20 mg/ml for **acetaminophen** calcium salt, cf. 0.02 mg/ ml for the free acid (control).

Dwg.0/2
FS CPI
FA AB; GI; DCN
MC CPI: B05-A01A; B05-A01B; B05-C01; B06-H; B07-H; B14-C01; B14-E10; B14-J01B1; B14-K01B; B14-K01D; B14-K01E; B14-L09; B14-N08
TECH UPTX: 20000313
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The alkali metal is selected from Na, K, Cs and Li. The alkaline earth metal is selected from Ca and Mg. (I) is in hydrated or anhydrous form. The analgesic is selected from e.g. acetyl salicylic acid, indomethacin, ibuprofen (racemates or optically active isomers), naproxen, flurbiprofen sulindac or codeine. The decongestant is selected from pseudoephedrine, phenylpropanolamine, phenylephrine and ephedrine. The expectorant is selected from e.g. guaifenesin, ambroxol and domiodol. The antitussive is selected from e.g. dextromethorphan, caramiphen and bezonatate. The antihistamine is selected from e.g. brompheniramine, fexofenadine and loratidine. The gastrointestinal agent is selected from e.g. atropine, clidinium and dicyclomine. The diuretic is selected from caffeine and pamabrom. The bronchodilator is selected from e.g. terbutaline, pinephrine and isoprenaline. The sleep-inducing agent is selected from e.g. melatonin, estazolam and zolpidem.

ABEX UPTX: 20000313
ADMINISTRATION - Administration may be oral and in a dose of 80-1000 mg (**acetaminophen** free acid basis).

L107 ANSWER 2 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1996-251055 [25] WPIX
CR 1993-190047 [24]
DNC C1996-079425
TI Compsn. for treating pain or as an antitussive - comprises ibuprofen and **tramadol.**
DC B05
IN **RAFFA, R B**
PA (MCNI) **MCNEILAB INC**
CYC 1
PI US 5516803 A 19960514 (199625)* 7 A61K031-19
ADT US 5516803 A CIP of US 1991-785137 19911030, Cont of US 1992-974863 19921110, US 1995-397022 19950301
PRAI US 1992-974863 19921110; US 1991-785137 19911030; US 1995-397022 19950301
IC ICM A61K031-19
ICS A61K031-135
AB US 5516803 A UPAB: 19960625
Compsn. comprises a **tramadol** material (I) and ibuprofen (II) in a weight ratio of 1:1-200.
The compsn. pref. further comprises a carrier, an antitussive, a muscle relaxant, a deep and a decongestant or bronchodilation and or an antihistamine (opt. non-sedating).
USE - The compsns. are used as antitussive and to control pain. They may also contain other ingredients e.g. decongestants, bronchodilators, antitussives, antihistamines of muscle relaxants or may be combined with **tramadol/acetaminophen** formulations for treating allergies, sleep disorders, cold, cough, cold-like and/or flu symptoms.
ADVANTAGE - The compsns. have less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. (I) and (II) are synergistic.
Dwg.0/1
FS CPI
FA AB; DCN
MC CPI: B10-B03B; B10-C04C; B14-C01; B14-C03; B14-K01B

L107 ANSWER 3 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1994-255297 [31] WPIX
CR 1993-100637 [12]
DNC C1994-116765
TI Synergistic combination of a **tramadol** material and **acetaminophen** - for treating pain and tussive conditions, has fewer side effects than when each component is used alone..
DC B05
IN **RAFFA, R B; VAUGHT, J L**
PA (MCNI) **MCNEILAB INC**
CYC 1
PI US 5336691 A 19940809 (199431)* 8 A61K031-165
ADT US 5336691 A CIP of US 1991-755924 19910906, US 1992-974865 19921110
PRAI US 1991-755924 19910906; US 1992-974865 19921110
IC ICM A61K031-165
AB US 5336691 A UPAB: 19940921
A pharmaceutical compsn. comprises a **tramadol** substance and **acetaminophen** in weight ratio 1:1-1:1600.
The **tramadol** is **tramadol** hydrochloride, which is especially racemic. The weight ratio tramedol:aminoacetophen is 1:5-1:1600, especially 1:19-1:800, especially pref. 1:19-1:50.
USE/ADVANTAGE - The combination can be used to treat pain and tussive

conditions. Suitable daily doses are 10-6000 mg/kg active ingredients. The mixture is synergistic and smaller amts. of each component can be used than when they are used alone thus the risk of side effects is reduced. The compsns. are subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression.
Dwg.0/1

FS CPI
FA AB; DCN
MC CPI: B10-B03B; B10-E02; B14-C01; B14-N17; B14-S09

L107 ANSWER 4 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1993-100637 [12] WPIX
CR 1994-255297 [31]
DNC C1993-044353
TI Synergistic combination of **tramadol** and **acetaminophen** - for treating pain and tissue conditions.
DC B05
IN **RAFFA, R B; VAUGHT, J L**
PA (MCNI) **MCNEILAB INC**; (ORTH) **ORTHO-MCNEIL PHARM INC**; (JOHJ) JOHNSON & JOHNSON
CYC 42
PI WO 9304675 A1 19930318 (199312)* EN 19 A61K031-16
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA SE
W: AU BB BG BR CA FI HU JP KP KR LK MG MW NO RO RU SD
AU 9225799 A 19930405 (199330) A61K031-165
EP 566709 A1 19931027 (199343) EN A61K031-16
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE
HU 64838 T 19940328 (199417) A61K031-16
JP 06502869 W 19940331 (199418) A61K031-135
ZA 9207434 A 19940525 (199423)# 19 A61K000-00
AU 651247 B 19940714 (199432) A61K031-165
NZ 244507 A 19940927 (199438)# A61K031-165
TW 242562 A 19950311 (199521) A61K031-135
CN 1086133 A 19940504 (199528) A61K031-165
EP 566709 A4 19940406 (199530) A61K031-16
IL 103313 A 19970610 (199730)# A61K031-13
EP 566709 B1 19980812 (199836) EN A61K031-16
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE
DE 69226624 E 19980917 (199843) A61K031-16
ES 2120451 T3 19981101 (199851) A61K031-16
CN 1198929 A 19981118 (199914)# A61K031-165
PH 29613 A 19960415 (200012)# A61K031-165
RU 2121346 C1 19981110 (200013) A61K031-085
MX 187871 B 19980123 (200046)# A61K031-005
KR 243956 B1 20000302 (200122) A61K031-13
HU 219332 B 20010328 (200124) A61K031-16
SG 80535 A1 20010522 (200134) A61K031-16
JP 3381190 B2 20030224 (200317) 11 A61K031-135
CA 2095523 C 20040622 (200442) EN A61K031-505
CN 1071571 C 20010926 (200509)# A61K031-166
ADT WO 9304675 A1 WO 1992-US7542 19920903; AU 9225799 A AU 1992-25799 19920903; EP 566709 A1 EP 1992-919762 19920903, WO 1992-US7542 19920903; HU 64838 T WO 1992-US7542 19920903, HU 1993-1313 19920903; JP 06502869 W WO 1992-US7542 19920903, JP 1993-505447 19920903; ZA 9207434 A ZA 1992-7434 19920928; AU 651247 B AU 1992-25799 19920903; NZ 244507 A NZ 1992-244507 19920925; TW 242562 A TW 1992-108965 19921110; CN 1086133 A CN 1992-112594 19921024; EP 566709 A4 EP 1992-919762 ; IL 103313 A IL 1992-103313 19921001; EP 566709 B1 EP 1992-919762 19920903, WO 1992-US7542 19920903; DE 69226624 E DE 1992-626624 19920903, EP 1992-919762 19920903, WO 1992-US7542 19920903; ES 2120451 T3 EP 1992-919762 19920903; CN 1198929 A Div ex CN 1992-112594 19921024, CN 1998-107417 19980420; PH 29613 A PH 1993-45661 19930202; RU 2121346 C1 RU 1993-43625 19920903; MX 187871 B MX 1992-5702 19921005; KR 243956 B1 WO 1992-US7542 19920903, KR 1993-701352

19930506; HU 219332 B WO 1992-US7542 19920903, HU 1993-1313 19920903; SG 80535 A1 SG 1996-5733 19920903; JP 3381190 B2 WO 1992-US7542 19920903, JP 1993-505447 19920903; CA 2095523 C CA 1992-2095523 19920903, WO 1992-US7542 19920903; CN 1071571 C CN 1992-112594 19921024

FDT AU 9225799 A Based on WO 9304675; EP 566709 A1 Based on WO 9304675; HU 64838 T Based on WO 9304675; JP 06502869 W Based on WO 9304675; AU 651247 B Previous Publ. AU 9225799, Based on WO 9304675; EP 566709 B1 Based on WO 9304675; DE 69226624 E Based on EP 566709, Based on WO 9304675; ES 2120451 T3 Based on EP 566709; HU 219332 B Previous Publ. HU 64838, Based on WO 9304675; JP 3381190 B2 Previous Publ. JP 06502869, Based on WO 9304675; CA 2095523 C Based on WO 9304675

PRAI US 1991-755924 19910906; ZA 1992-7434 19920928;
NZ 1992-244507 19920925; IL 1992-103313 19921001;
CN 1998-107417 19980420; PH 1993-45661 19930202;
MX 1992-5702 19921005

REP 1.Jnl.Ref; US 3652589; No-Citns.

IC ICM A61K000-00; A61K031-005; A61K031-085; A61K031-13; A61K031-135; A61K031-16; A61K031-165; A61K031-166; A61K031-505
ICS **A61K031-167**; A61K031-485; A61P025-04; A61P029-02

ICA C07C217-54

AB WO 9304675 A UPAB: 20050207
New compsn. comprises a **tramadol** (I) material, **acetaminophen** (II) and opt. a carrier.

Pref. (I) material includes (I), its N-oxide and O-desmethyl derivs. and mixts. of these; isomers, mixts of these and racemates; and salts, solvates and polymorphs. Racemic (I HCl) is pref. (I) is described in US Pat. 3,652,589.

USE/ADVANTAGE - The compsn. is analgesic and is useful for treatment of pain and tussive conditions. An effective dose requires less of both (I) and (II) than when using (I) or (II) alone, with a corresp. reduction of side effects (including opioid side effects (e.g. abuse liability, toleration, constipation and respiratory depression)). Certain ratios of (I) and (II) are synergistic.

Admin. is oral or parenteral at a unit dose containing 0.1-800 mg/kg, pref. 0.3-200 mg/kg active ingredients.ti
Dwg.0/1
Dwg.0/1

FS CPI

FA AB; DCN

MC CPI: B10-A03; B10-B03B; B10-D03; B12-C09; B12-D01; B12-K01

ABEQ EP 566709 A UPAB: 19931207
New compsn. comprises a **tramadol** (I) material, **acetaminophen** (II) and opt. a carrier.

Pref. (I) material includes (I), its N-oxide and O-desmethyl derivs. and mixts. of these; isomers, mixts of these and racemates; and salts, solvates and polymorphs. Racemic (I HCl) is pref. (I) is described in US Pat. 3,652,589.

USE/ADVANTAGE - The compsn. is analgesic and is useful for treatment of pain and tussive conditions. An effective dose requires less of both (I) and (II) than when using (I) or (II) alone, with a corresp. redn. of side effects (including opioid side effects (e.g. abuse liability, toleration, constipation and respiratory depression)). Certain ratios of (I) and (II) are synergistic.

Admin. is oral or parenteral at a unit dose contg. 0.1-800 mg/kg, pref. 0.3-200 mg/kg active ingredients.

=> => fil uspatful
FILE 'USPATFULL' ENTERED AT 08:26:20 ON 06 APR 2005
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 5 Apr 2005 (20050405/PD)
FILE LAST UPDATED: 5 Apr 2005 (20050405/ED)

HIGHEST GRANTED PATENT NUMBER: US6877166
HIGHEST APPLICATION PUBLICATION NUMBER: US2005071904
CA INDEXING IS CURRENT THROUGH 5 Apr 2005 (20050405/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 5 Apr 2005 (20050405/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2005

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>>> /PK, etc. <<<

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>>> enter this cluster. <<<
>>> <<<
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>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d bib abs kwic hitstr tot

L117 ANSWER 1 OF 10 USPATFULL on STN
AN 2002:112901 USPATFULL
TI Analgesic and glucosamine compositions
IN **Raffa, Robert**, Norristown, PA, UNITED STATES
Cowan, Alan, Ambler, PA, UNITED STATES
Tallarida, Ronald, Mantua, NJ, UNITED STATES
PA Temple University of the Commonwealth of Higher corporation)
PI US 2002058642 A1 20020516
AI US 2001-964178 A1 20010925 (9)
PRAI US 2000-235405P 20000926 (60)
DT Utility
FS APPLICATION
LREP Robert L. Andersen, Ratner & Prestia, One Westlakes, Berwyn, Suite 301, P.O. Box 980, Valley Forge, PA, 19482-0980
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 3 Drawing Page(s)
LN.CNT 678
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a composition comprising a glucosamine material and an analgesic compound such as a nonsteroidal anti-inflammatory drug (NSAID) and/or an opioid analgesic and its use for treatment of pain in pharmaceutical or veterinary applications. When the components of the compositions are administered within certain ratios, the analgesic efficacy of the composition is super-additive (synergistic) relative to the analgesic efficacy of the analgesic compound alone.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IN **Raffa, Robert**, Norristown, PA, UNITED STATES

There may be some "false" hits in this set → full text file

SUMM [0003] Drugs such as aspirin, ibuprofen, **acetaminophen**, and morphine are used as analgesics. Ibuprofen, aspirin and other analgesic nonsteroidal anti-inflammatory drugs (commonly referred to as NSAIDs) and **acetaminophen** are only useful in relieving pain of moderate intensity, whereas opioid analgesics such as morphine are useful in relieving more intense pain. However, opioids exhibit side-effects including addictive properties, and ibuprofen, aspirin, other NSAIDs and **acetaminophen** can cause serious gastrointestinal, renal, and cardiovascular side effects, especially when used in high doses and/or over long periods of. . .

SUMM . . . ratios. A. Pircio et al., Arch. Int. Pharmacodyn., 235,116 (1978) report that a mixture of butorphanol (an opioid analgesic) with **acetaminophen** (a non-opioid analgesic) in a 1:125 ratio yielded super-additive analgesia, but that a 1:10 mixture of the same components yielded merely additive analgesic effects. A combination of tolmetin (an NSAID) with **acetaminophen** (a non-opioid analgesic) has been reported to enable a marked reduction in the amount of tolmetin required to produce analgesia. . .

SUMM . . . the contrary, it has been shown that when glucosamine is combined at certain ratios, for example with aspirin, diclofenac or **tramadol** (a centrally acting non-opioid analgesic), the analgesic efficacy of analgesic is reduced (i.e., the combination is sub-additive) by as much. . .

SUMM . . . analgesic effects which can occur when two or more analgesics are combined or when an analgesic, such as diclofenac or **tramadol**, is combined with glucosamine. In the preferred embodiment, the combination of glucosamine with an analgesic compound at an appropriate ratio. . .

DETD Preparation of the Combined Doses of Glucosamine and **Tramadol**

DETD [0028] Solutions of glucosamine/**tramadol** combinations with different ratios were prepared and concentrations of each component expressed as mg per 10 mL of distilled water. For example, 250 mg of glucosamine sulfate and 10 mg of **tramadol** HCL were added to 10 mL of water with 2 drops of TWEEN®-80, a pharmacological dispersant, to yield a glucosamine sulfate to **tramadol** weight ratio of 25:1 (250 mg: 10 mg), which corresponds to a glucosamine to **tramadol** weight ratio of about 15:1.

DETD Preparation of the Combined Doses of Glucosamine and **Acetaminophen**

DETD [0029] Solutions of glucosamine/**acetaminophen** combinations with different ratios were prepared and concentrations of each component expressed as mg per 10 mL of distilled water. For example, 112.5 mg of glucosamine sulfate and 112.5 mg of **acetaminophen** were added to 10 mL of water with 2 drops of TWEEN®-80, a pharmacological dispersant, to yield a glucosamine sulfate to **acetaminophen** weight ratio 1:1 (112.5 mg:112.5 mg), which corresponds to a glucosamine to **acetaminophen** weight ratio of about 0.58:1.

DETD . . . were all dosed orally with glucosamine sulfate, which was completely dissolved in distilled water, and a selected analgesic (ibuprofen, diclofenac, **tramadol** HCl, or **acetaminophen**), which was completely dissolved in distilled water or in distilled water containing 2% by volume of TWEEN®-80 containing 100% polysorbate. . .

DETD [0043] Table 4 shows the results of assays of combinations of aspirin and glucosamine sulfate, **acetaminophen** and glucosamine sulfate, diclofenac and glucosamine sulfate, **tramadol** HCl and glucosamine sulfate, and indomethacin and glucosamine sulfate. Treatment doses were selected based on the ED50 for each analgesic. . .

DETD [0045] For **acetaminophen** alone compared **acetaminophen** in combination with glucosamine sulfate, the data demonstrate that **acetaminophen** does not exhibit a super-additive analgesic effect in combination with glucosamine sulfate, in general appears to exhibit sub-additive analgesia, but. . .

DETD [0046] Similarly, when either diclofenac or **tramadol** HCl was combined with glucosamine sulfate, the analgesic efficacy of either analgesic compound was substantially reduced at the ratios tested.. . . when administered in combination with glucosamine sulfate at the concentrations tested, a clear case of sub-additivity. As another example, when **tramadol** HCl was used in combination with glucosamine sulfate, the analgesic efficacy of **tramadol** HCl was reduced such that the 50% effect level (5/10 animals protected) could not be achieved even with the combination containing 10 mg/kg of **tramadol** HCl, a **tramadol** HCl dosage greater than the ED50=8.05 mg/kg value of **tramadol** HCl when used alone, i.e., another clear case of sub-additivity. Thus, combinations of glucosamine with aspirin, **acetaminophen**, diclofenac or tramidol at those ratios are sub-additive and thus are, by definition, excluded from the scope of the invention. . .

DETD . . . mg/kg.sup.(a)

ASA	Glucosamine	No. protected/no. tested
50	--	1/10
100	--	4/10
150	--	8/10
200	--	7/10
50	125	2/10
100	250	2/10
150	375	1/10
200	500	2/10

Acetaminophen, mg/kg + Glucosamine sulfate, mg/kg

Acetaminophen	Glucosamine	No. protected/no. tested
62.5	--	1/10
125	--	4/10
250	--	8/10
28.12	28.12	1/10
56.25	56.25	2/10
62.5	62.5	1/10
93.75	93.75	0/10
112.5	112.5	5/10
125. . . 50	5/10	
25	100	0/10
50	200	0/10
100	400	1/10

Diclofenac, mg/kg + Glucosamine sulfate, mg/kg.sup.(b)

Diclofenac	Glucosamine	No. protected/no, tested
1.144	125	5/20
2.288	250	6/10

Tramadol HCl, mg/kg + Glucosamine sulfate, mg/kg.sup.(c)

Tramadol	Glucosamine	No. protected/no. tested
6	150	1/10
10	250	3/10

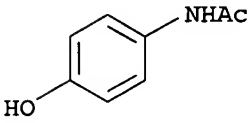
Indomethacin, mg/kg + Glucosamine sulfate, mg/kg.sup.(d)

Indomethacin	Glucosamine	No. protected/no. tested
2.5	--	4/10

5.0. . .

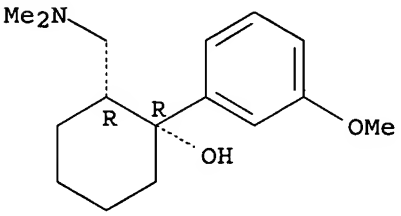
IT 66-84-2, Glucosamine hydrochloride **103-90-2**, Acetaminophen 3416-24-8, Glucosamine 7512-17-6, N-Acetylglucosamine 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 22071-15-4, Ketoprofen

27203-92-5, Tramadol 29031-19-4, Glucosamine sulfate
(analgesic and glucosamine compns.)
IT **103-90-2**, Acetaminophen **27203-92-5**, Tramadol
(analgesic and glucosamine compns.)
RN 103-90-2 USPATFULL
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



RN 27203-92-5 USPATFULL
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L117 ANSWER 2 OF 10 USPATFULL on STN
AN 1998:39530 USPATFULL
TI **Acetaminophen** and dimenhydrinate analgesics
IN Hough, Douglas R., Morrisville, PA, United States
Nelson, Edward B., Lower Gwynedd, PA, United States
Raffa, Robert B., Norristown, PA, United States
PA McNeil-PPC, Inc., Skillman, NJ, United States (U.S. corporation)
PI US 5739139 19980414
AI US 1996-667054 19960620 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Reamer, James H.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 317
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are compositions comprising **acetaminophen** (APAP) and dimenhydrinate and methods for their use in analgesia. When **acetaminophen** and dimenhydrinate are within certain ratios, their pharmacological effects are superadditive.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Acetaminophen** and dimenhydrinate analgesics
IN **Raffa, Robert B.**, Norristown, PA, United States
AB Disclosed are compositions comprising **acetaminophen** (APAP) and dimenhydrinate and methods for their use in analgesia. When **acetaminophen** and dimenhydrinate are within certain ratios, their pharmacological effects are superadditive.
SUMM The present invention relates to analgesic compositions. More particularly, the present invention relates to analgesic compositions containing **acetaminophen** and dimenhydrinate.

SUMM **Acetaminophen**, N-(**4-hydroxyphenyl**)
acetamide or herein referred to as APAP, was first used in medicine by Van Mering in 1893, but only since 1949. . .

SUMM . . . when combined with APAP or aspirin exhibit superadditive antiarthritic activity. Also, U.S. Pat. No. 5,336,691 discloses that the combination of **tramadol**, a centrally active analgesic, and APAP exhibits a synergistic analgesic effect when combined in certain ratios. G. B. Pat. No.. . .

DETD (a) an analgesic inducing amount of **acetaminophen**;

DETD . . . from about 1/20 to about 1/500 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**; and

DETD . . . In a preferred embodiment of the present invention, the dimenhydrinate is present only to enhance the analgesic effect of the **acetaminophen**. In such case, the dimenhydrinate should be present in an amount insufficient to produce substantial relief from motion sickness or. . .

DETD TABLE 1

Mouse Acetylcholine-Bromide Induced
Abdominal Constriction Assay
Acetaminophen (APAP) and HCl salt of Dimenhydrinate (DMHD)
Dose # of mice ED.sub.50 at 30 min
(mg/kg, p.o.)
with no (95%. . .

CLM What is claimed is:
1. A composition for use as an analgesic comprising: (a) an analgesic inducing amount of **acetaminophen**; (b) from about 1/20 to about 1/500 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**; and (c) a pharmaceutically acceptable carrier.

. . . from about 1/50 to about 1/200 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**.

. . . claim 1 which comprises about 1/100 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**.

4. The composition of claim 1 in a dosage form containing 10 to 2000 mg of **acetaminophen**.

5. The composition of claim 1 in a dosage form containing 25 to 1000 mg of **acetaminophen**.

6. The composition of claim 1 in a dosage form containing 100 to 500 mg of **acetaminophen**.

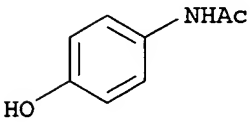
8. The composition of claim 1 which contains a sufficient amount of surface active agent to stabilize a suspension of the **acetaminophen**.

. . . for inducing analgisia in a mammal comprising the step of administering a combination comprising: (a) an analgesic inducing amount of **acetaminophen**; (b) from about 1/20 to about 1/500 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**; and (c) a pharmaceutically acceptable carrier.

. . . from about 1/50 to about 1/200 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen**.

. . . wherein said combination comprises about 1/100 parts by weight dimenhydrinate or pharmaceutically acceptable salt thereof for each part by weight **acetaminophen.**

IT **103-90-2**, Acetaminophen 523-87-5, Dimenhydrinate
(synergistic analgesic combination containing acetaminophen and dimenhydrinate)
IT **103-90-2**, Acetaminophen
(synergistic analgesic combination containing acetaminophen and dimenhydrinate)
RN 103-90-2 USPATFULL
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



L117 ANSWER 3 OF 10 USPATFULL on STN
AN 96:41241 USPATFULL
TI Composition comprising a **tramadol** material and a non-steroidal anti-inflammatory drug
IN **Raffa, Robert B.**, Norristown, PA, United States
PA McNeilab, Inc., Spring House, PA, United States (U.S. corporation)
PI US 5516803 19960514
AI US 1995-397022 19950301 (8)
RLI Continuation of Ser. No. US 1992-974863, filed on 10 Nov 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-785137, filed on 30 Oct 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Henley, III, Raymond
LREP Palo, Ralph R.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 552
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a composition comprising a **tramadol** material and a nonsteroidal antiinflammatory drug, and its use. The compositions are pharmacologically useful in treating pain and tussive conditions. The compositions are also subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compositions are within certain ratios the pharmacological effects of the compositions are superadditive (synergistic).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Composition comprising a **tramadol** material and a non-steroidal anti-inflammatory drug
IN **Raffa, Robert B.**, Norristown, PA, United States
AB This invention relates to a composition comprising a **tramadol** material and a nonsteroidal antiinflammatory drug, and its use. The compositions are pharmacologically useful in treating pain and tussive conditions.. . .
SUMM . . . of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1R, 2R or 1S, 2S)-**2**-[(**dimethylamino**)**methyl**]-**1**-(**3**-**methoxyphenyl**)-**cyclohexanol**, commonly

known as **tramadol**, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of **tramadol** are found in Arzneim, Forsch. (Drug Res.), 28(I), 114 (1978). Driessen et al., Arch. Pharmacol., 341, R104 (1990) disclose that **tramadol** produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the Vlth World Congress on Pain, Apr. 1-6 (1990), disclose that **tramadol** hydrochloride is an orally active pure agonist opioid analgesic. However, clinical experience indicates that **tramadol** lacks many of the typical side effects of opioid agonists, e.g., respiratory depression (W. Vogel et al., Arzneim Forsch. (Drug. . . Yanagita, Arzneim. Forsch. (Drug Res.), 28(I), 158 (1978)). When given at a dose of 50 mg by rapid i.v. injection, **tramadol** may produce certain side effects unique to **tramadol** including hot flushes and sweating. Despite these side effects, **tramadol**'s combination of non-opioid and opioid activity makes **tramadol** a very unique drug. **Tramadol** is currently being marketed by Grunenthal GMBH as an analgesic.

SUMM As alternatives to using opioids, non-opioids such as **acetaminophen**, aspirin and ibuprofen are used as analgesics. Ibuprofen, like aspirin, is not subject to the tolerance, addiction and toxicity of. . .

SUMM . . . al., Arch. Int. Pharmacodyn., 235, 116 (1978) report superadditive analgesia with a 1:125 mixture of butorphanol, another opioid analgesic, and **acetaminophen**, a non-opioid analgesic, whereas a 1:10 mixture did not show any statistically significant superadditive analgesia.

SUMM . . . Int. J. Clin. Pharmacol. Biopharmacy, 17, 250 (1979) report that the combination of non-opioid analgesics, i.e., tolmetin (another NSAID) and **acetaminophen**, allows for a marked reduction in the amount of tolmetin required to produce analgesia. In addition, U.S. Pat. No. 4,260,629 discloses that an orally administered composition of **acetaminophen** and zomepirac, a non-opioid analgesic, in a particular weight ratio range produces a superadditive relief of pain in mammals. Furthermore, U.S. Pat. No. 4,132,788 discloses that 5-aroyl-1-(lower)alkylpyrrole-2-acetic acid derivatives, non-opioid analgesics, when combined with **acetaminophen** or aspirin exhibit superadditive antiarthritic activity. However, there have been warnings against the daily consumption of non-opioid analgesic mixtures and. . .

SUMM The prior art, however, does not disclose that **tramadol**, an `atypical` opioid analgesic, can or should be combined with another analgesic to lessen the side effects of each or to yield a composition comprising a **tramadol** material and another analgesic that exhibits superadditive analgesia.

SUMM It has now been found that a **tramadol** material which includes various forms of **tramadol** as defined hereinafter can be combined with nonsteroidal antiinflammatory drugs (hereinafter NSAIDs) to produce analgesia. The combination employs lesser amounts of both the **tramadol** material and the NSAID than would be necessary to produce the same amount of analgesia if either was used alone.. . . of both drugs the side effects associated with each are reduced in number and degree. Surprisingly, the compositions comprising the **tramadol** material and one or more NSAIDs have been found to exhibit synergistic analgesic effects when combined in certain ratios. Particularly preferred compositions are those comprising a **tramadol** material and ibuprofen. The compositions according to this invention may also be useful in treating tussive conditions.

DRWD FIG. 1 is an isobologram showing the analgesic effect of **tramadol** hydrochloride and ibuprofen composition on the acetylcholine-induced abdominal constriction in mice.

DETD The present invention is generally directed to compositions comprising a **tramadol** material and an NSAID. The **tramadol** material

is any one of (1R, 2R or 1S, 2S)-2-[(**dimethylamino**) **methyl**]-1-(3-**methoxyphenyl**) **cyclohexanol** (**tramadol**), its N-oxide derivative ("**tramadol** N-oxide"), and its O-desmethyl derivative ("O-desmethyl **tramadol**") or mixtures thereof. It also includes the individual stereoisomers, mixtures of stereoisomers, including the racemates, pharmaceutically acceptable salts of the amines, such as the hydrochloride salt, solvates and polymorphs of the **tramadol** material. **Tramadol** is commercially available from Grunenthal or may be made by the process described in U.S. Pat. No. 3,652,589, which is. . .

DETD **Tramadol** N-oxide is prepared by treating **tramadol** as a free base with an oxidizing agent, e.g., hydrogen peroxide (30%), in an organic solvent, e.g., methanol or isopropanol,. . .

DETD O-desmethyl **tramadol** is prepared by treating **tramadol** as a free base under O-demethylating reaction conditions, e.g., reacting it with a strong base such as NaH or KH,. . .

DETD . . . proquazone), phenylacetic acid derivatives such as diclofenac; etodolac and nabumetone. For the purposes of this invention, para-aminophenol derivatives such as **acetaminophen** are not considered NSAIDs because of their general lack of antiinflammatory activity. All of the NSAIDs are commercially available materials.. . .

DETD The NSAID and the **tramadol** material are generally present in a weight ratio of **tramadol** material to NSAID from about 1:1 to 1:200. Certain ratios result in a composition which exhibits synergistic analgesic effects. For example, in a composition comprising a **tramadol** material and an NSAID, the ratio of the **tramadol** material: NSAID is preferably from about 1:1 to 1:200; and, more preferably, from about 1:2 to 1:200. The most preferred ratios are from about 1:2 to 1:20. Compositions of a **tramadol** material and an NSAID within these weight ratios have been shown to exhibit synergistic analgesic effects.

DETD A particularly preferred composition according to the present invention is a **tramadol** material and ibuprofen. The ratio of the **tramadol** material to ibuprofen in this preferred combination is from about 1:1 to 1:200, more preferably from about 1:2 to 1:200. . .

DETD The **tramadol**/NSAID formulations according to the present invention may also contain therapeutically effective amounts of one or more other pharmaceutical actives including. . . pharmaceutically acceptable salts thereof) and combinations of any of the aforesaid pharmaceuticals. The aforesaid pharmaceuticals may be combined with a **tramadol**/**acetaminophen** formulation for the treatment of such ailments as allergies, sleep disorders, cough, colds, cold-like and/or flu symptoms in mammals including. . .

DETD Pharmaceutical compositions comprising the **tramadol** material and the NSAID and when desired other pharmaceutical actives in an intimate admixture with a pharmaceutical carrier can be. . . it will be appreciated that the precise dose of the active ingredients will vary depending upon the particular NSAID and **tramadol** material being used. In the case wherein one or more other pharmaceutical components are added to the **tramadol**/NSAID composition those components may be added in therapeutically effective amounts known in the art and may be given at dosages. . .

DETD Preparation of the Combined Doses of **Tramadol** and Ibuprofen

DETD The preparation of different ratios of a **tramadol**/ibuprofen combination was effected by preparing solutions having concentrations expressed in mg.sub.drugs per 10 mL of distilled water. For example, 40 mg of **tramadol** as the free base and 40 mg of ibuprofen as the free base were added to 10 mL of water. . . 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the highest concentration of the **tramadol**/ibuprofen 1:1 (40mg:40mg) ratio. Each concentration of the ratio was prepared separately in a similar manner and injected in a volume of 10 mL/kg per

mouse. Similarly, the other ratios of **tramadol**/ibuprofen listed in Table 1 were prepared at the various concentrations.

DETD Preparation of the Combined Doses of **Tramadol** N-oxide and Ibuprofen

DETD First, **tramadol** N-oxide was prepared as set forth hereinafter. **Tramadol** hydrochloride (0.5 mol) was converted to its free base in basified water (pH>9) and then extracted with ether. The ether was evaporated to yield the crystalline hydrate of **tramadol.** The solid was then heated with steam under a high vacuum to remove as much water as possible to yield. . . The solid was collected by filtration, washed with ethyl acetate and dried in vacuo to yield 126.6 g of the **tramadol** N-oxide (mp. 159.5°-160° C.).

DETD The preparation of different ratios of a **tramadol** N-oxide/ibuprofen combination is effected by preparing solutions having concentrations expressed in mg.sub.drugs per 10 mL of distilled water. For example, 40 mg of **tramadol** as the free base and 40 mg of ibuprofen as the free base is added to 10 mL of water. . . 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the highest concentration of the **tramadol** N-oxide/ibuprofen 1:1 (40mg:40mg) ratio. Each concentration of the ratio is prepared separately in a similar manner.

DETD (-) and (+) Enantiomers of O-Desmethyl **Tramadol**: Their Syntheses and the Preparation of Doses of O-Desmethyl **Tramadol** with Ibuprofen

DETD First, O-desmethyl **tramadol** was prepared as set forth hereinafter. Diethylene glycol (125 mL) was added with cooling to potassium hydride (9.5 g) with. . . maintained at <50° C. To the solution was added thiophenol (10 mL) dissolved in diethylene glycol (25 mL), and then (-)-**tramadol** as the free base (9.3 g) in diethylene glycol (50 mL) was added. The final reaction mixture was heated slowly. . . was recrystallized from ethanol/ethyl ether and dried to yield 1.80 g of the salt of the (-) enantiomer of O-desmethyl **tramadol** (mp. 242°-3° C.), [α].sub.D.sup.25 =-32.9 (C=1, EtOH).

DETD To prepare the (+) enantiomer of the title compound, the reaction was run under the same conditions except that (+)-**tramadol** as the free base was used instead of the (-)-**tramadol** to yield 2.8 g of the (+) enantiomer of O-desmethyl **tramadol** (mp. 242°-3° C.) [α].sub.D.sup.25 =+32.2 (C=1, EtOH).

DETD . . . drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the highest concentration of the O-desmethyl **tramadol**/ibuprofen 1:1 (40mg:40mg) ratio. Each concentration of the ratio is prepared separately in a similar manner and injected in a volume. . .

DETD . . . utilized in determining the analgesic effects associated with the compositions of the invention. The mice were all dosed orally with **tramadol** hydrochloride (calculated as the base), which was completely dissolved in distilled water, and ibuprofen (calculated as the base), which was. . .

DETD Mice, incubated with various doses of **tramadol** hydrochloride alone, ibuprofen alone, combined doses of **tramadol** hydrochloride and ibuprofen, or vehicle such as distilled water, or distilled water containing 2% by volume of Tween 80, were. . . abdominal constriction response beginning immediately after receiving the acetylcholine dose, which was 30 minutes after receiving the oral administration of **tramadol** hydrochloride, ibuprofen, combined doses of **tramadol** hydrochloride and ibuprofen, or vehicle. Each mouse was used only once.

DETD . . . for the two drugs under additivity. ED50.sub.mix was then compared to ED50.sub.add via a Student's t-test. The ED50 value for **tramadol** hydrochloride alone was 5.5(4.8-6.4) mg/kg. The ED50 value for ibuprofen alone was 33.5 (24.1-46.5) mg/kg.

DETD The interaction between **tramadol** and ibuprofen was determined

at precise dosage ratios of **tramadol** hydrochloride and ibuprofen. Multiple (typically 4-6) coded doses of each selected combination were studied for analgesic effectiveness after 30 minutes. . .

DETD The interaction of **tramadol** hydrochloride and ibuprofen on the acetylcholine-induced abdominal constriction in mice was demonstrated by the data in Table I and is. . . i.e., unexpected enhancement of effects. The diagonal dashed lines radiating from the origin represent the dose ratios of ibuprofen to **tramadol** hydrochloride used in mice receiving the combined drug dosages. The bars through the ED50 points for the **tramadol** and ibuprofen composition represent the 95% confidence intervals of the ED50 value. The experimental data as represented in FIG. I establish that compositions having a ratio of **tramadol** to ibuprofen from about 1:1 to 1:200 (represented by the curved line) give unexpectedly enhanced activity since ED50.sub.mix is less. . .

DETD It is expected that based on these results, other NSAIDs, and particularly the propionic acid derivatives, when combined with a **tramadol** material, will produce similar synergistic results.

DETD TABLE I

TRAMADOL:IBUPROFEN DRUG COMBINATIONS (**Tramadol**:Ibuprofen)	DOSE (mg/kg, p.o.) **Tramadol**	Ibuprofen	ED.sub.50 at 30 min (95% Cl's) analgesia	**Tramadol**	Ibuprofen
tramadol only	2	0	3/15	5.5	--
	3	0	4/15	(4.8-6.4)	
	4	0	14/45		
	6	0	20/45		
	8	0	40/60		
	10. . .				

CLM What is claimed is:

1. A pharmaceutical composition comprising a **tramadol** material and ibuprofen, wherein the ratio of the **tramadol** material to the ibuprofen is a weight ratio of from about 1:1 to about 1:200.

2. The pharmaceutical composition of claim 1 wherein the **tramadol** material is tramado hydrochloride.

3. The pharmaceutical composition of claim 1 wherein the **tramadol** hydrochloride is racemic.

6. The pharmaceutical composition of claim 1, wherein the **tramadol** material is **tramadol** hydrochloride.

. . . comprising administering to the mammal an effective amount of a pharmaceutical composition for treating pain and tussive conditions comprising a **tramadol** material and ibuprofen, wherein the ratio of the **tramadol** material to the ibuprofen is a weight ratio of from about 1:1 to about 1:200.

. . . in a mammal comprising administering to the mammal an effective amount of a pharmaceutical composition for treating pain comprising a **tramadol** material and ibuprofen, wherein the ratio of the **tramadol** material to the ibuprofen is a weight ratio of from about 1:1 to about 1:200.

15. The method of claim 14, wherein the **tramadol** material is **tramadol** hydrochloride.

IT 53-86-1D, Indomethacin, mixts. with tramadol derivative 5104-49-4D, Flurbiprofen, mixts. with tramadol derivative 15687-27-1D, Ibuprofen, mixts. with tramadol derivative 21256-18-8D, Oxaprozin, mixts. with tramadol derivative 22071-15-4D, Ketoprofen, mixts. with tramadol derivative 22204-53-1D, Naproxen, mixts. with tramadol derivative **27203-92-5D**, Tramadol, mixts. with anti-inflammatory agent
(analgesic compns. containing, synergistic)

IT 34597-40-5D, Fenoprofen calcium, mixts. with tramadol derivative **36282-47-0D**, Tramadol hydrochloride, mixts. with anti-inflammatory agent 38194-50-2D, Sulindac, mixts. with tramadol derivative 154605-61-5
(analgesic compns. containing, synergistic)

IT **27203-92-5**, Tramadol
(oxidation of)

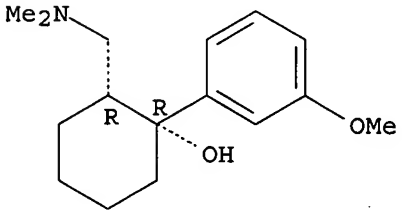
IT **144830-14-8P**, (+)-O-Desmethyltramadol **144830-15-9P**, (-)-O-Desmethyltramadol **147441-56-3P**, Tramadol N-oxide
(preparation of and synergic analgesic composition containing inflammation inhibitors and)

IT **27203-92-5D**, Tramadol, mixts. with anti-inflammatory agent **36282-47-0D**, Tramadol hydrochloride, mixts. with anti-inflammatory agent
(analgesic compns. containing, synergistic)

RN 27203-92-5 USPATFULL

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

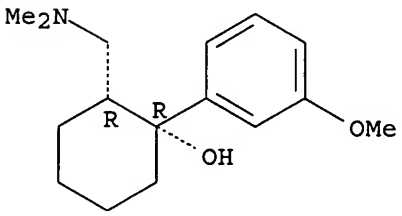
Relative stereochemistry.



RN 36282-47-0 USPATFULL

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

IT **27203-92-5**, Tramadol
(oxidation of)
RN 27203-92-5 USPATFULL
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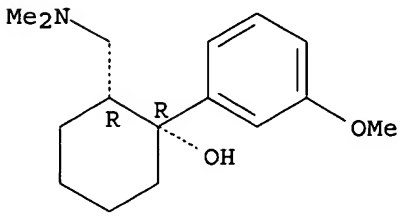
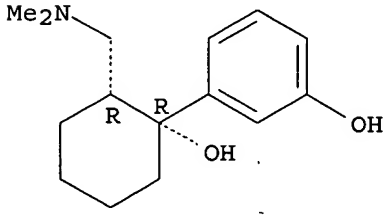
Relative stereochemistry.



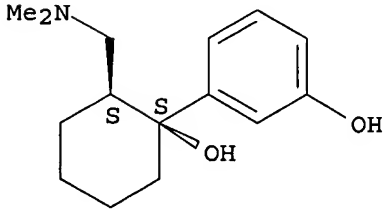
IT **144830-14-8P**, (+)-O-Desmethyltramadol **144830-15-9P**, (-)-O-Desmethyltramadol **147441-56-3P**, Tramadol N-oxide
(preparation of and synergic analgesic composition containing inflammation inhibitors
and)
RN 144830-14-8 USPATFULL
CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



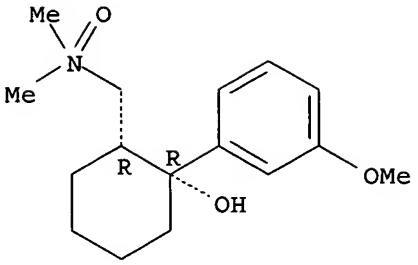
RN 144830-15-9 USPATFULL
CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 147441-56-3 USPATFULL
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L117 ANSWER 4 OF 10 USPATFULL on STN
AN 95:103506 USPATFULL
TI Composition comprising a **tramadol** material and any of codeine, oxycodone or hydrocodone and their use
IN **Raffa, Robert B.**, Norristown, PA, United States
Vaught, Jeffrey L., Perkasie, PA, United States
PA McNeil Lab, Inc., Spring House, PA, United States (U.S. corporation)
PI US 5468744 19951121
AI US 1994-268382 19940630 (8)
RLI Continuation of Ser. No. US 1992-976728, filed on 16 Nov 1992, now abandoned which is a continuation of Ser. No. US 1991-755923, filed on 6 Sep 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Henley, III, Raymond; Assistant Examiner: Jarvis, William R. A.
LREP Palo, Ralph R.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 504
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to compositions comprising a **tramadol** material selected from the group consisting of **tramadol**, its stereoisomers and its pharmaceutically acceptable salts and either codeine or oxycodone, and their use in treating pain. When the components, i.e., **tramadol** materials and either of codeine or oxycodone, of the composition are within certain ratios of pharmacological effects of the compositions are superaddditive (synergistic).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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IN **Raffa, Robert B.**, Norristown, PA, United States
IN **Vaught, Jeffrey L.**, Perkasie, PA, United States
AB This invention relates to compositions comprising a **tramadol** material selected from the group consisting of **tramadol**, its stereoisomers and its pharmaceutically acceptable salts and either codeine or oxycodone, and their use in treating pain. When the components, i.e., **tramadol** materials and either of codeine or oxycodone, of the composition are within certain ratios of pharmacological effects of the compositions. . .
SUMM . . . a class of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1RS, 2RS) trans-**2-[(dimethylamino)-methyl]-1-(3-methoxyphenyl)cyclohexanol**, commonly known as **tramadol**, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of **tramadol** are found in Arzneim, Forsch

(Drug Res.), 28(1), 114 (1978). Driessen et al., Arch. Pharmacol., 341, R104 (1990) disclose that **tramadol** produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the VI th World Congress on Pain, Apr. 1-6 (1990) discloses that **tramadol** hydrochloride is an orally active pure agonist opioid analgesic. However, clinical experience indicates that **tramadol** lacks many of the typical-side effects of opioid agonists, e.g., respiratory depression (W. Vogel et al., Arzneim, Forsch, (Drug Res.),. . . Yanagita, Arzneim, Forsch. (Drug Res.), 28(1), 158 (1978)). When given at a dose of 50 mg by rapid i.v. injection, **tramadol** may however, produce certain side effects unique to **tramadol** including hot flushes and sweating. Despite theses side effects, **tramadol**'s combination of non-opioid and opioid activity makes **tramadol** a very unique drug. **Tramadol** is currently being marketed by Grunenthal GMBH in Germany as an analgesic.

SUMM . . . al., Arch. Int. Pharmacodyn., 235, 116 (1978) report superadditive analgesia with a 1:125 mixture of butorphanol, another opioid analgesic, and **acetaminophen** (APAP), a non-opioid analgesic, whereas a 1:10 mixture did not show any statistically-significant superadditive analgesia.

SUMM However, the prior art, does not suggest or disclose that **tramadol**, an "atypical" opioid analgesic, can or should be combined with another analgesic, particularly an opioid analgesic, to lessen the side. . .

SUMM It has now been found that a **tramadol** material which includes various forms of **tramadol** as defined hereinafter can be combined with certain opioids, codeine, oxycodone and hydrocodone, to produce an analgesic effect. Each of. . . structure; i.e., each one has a 3-methoxy substituent on the aromatic moiety. The combination employs lesser amounts of both the **tramadol** material and the opioid than would be necessary to produce the same amount of analgesia if either was used alone.. . . of both drugs the side effects associated with each are reduced in number and degree. Surprisingly, the compositions comprising a **tramadol** material and any of codeine, oxycodone or hydrocodone have been found to exhibit synergistic analgesic effects when combined in certain. . .

DRWD FIG. 1 is an isobologram showing the analgesic effect of **tramadol** hydrochloride and codeine phosphate compositions on tail-flick latency in mice; and

DRWD FIG. 2 is an isobologram showing the analgesic effect of **tramadol** hydrochloride and oxycodone hydrochloride composition on tail-flick latency in mice.

DETD The present invention is directed to compositions comprising a **tramadol** material and any one of codeine, oxycodone or hydrocodone and mixtures thereof.

DETD The **tramadol** material according to the present invention is any one of (1R, 2R or 1S, 2S)-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol (**tramadol**), its N-oxide derivative ("**tramadol** N-oxide"), and its O-desmethylated derivative ("O-desmethyl **tramadol**") or mixtures thereof. It also includes the individual stereoisomers, mixtures of stereoisomers including the racemates, pharmaceutically acceptable salts of the amines, such as the hydrochloride salt, solvates and polymorphs thereof. **Tramadol** is commercially available from Grunenthal or may be made by the process described in U.S. Pat. No. 3,652,589, which is. . .

DETD **Tramadol** N-oxide is prepared by treating **tramadol** as a free base with an oxidizing agent, e.g., hydrogen peroxide (30%), in an organic solvent, e.g., methanol or isopropanol,. . .

DETD O-Desmethyl **tramadol** is prepared by treating **tramadol** as a free base under O-desmethylating reaction conditions, e.g., reacting it with a strong base such as NaH or KH,. . .

DETD The **tramadol** material and the opioid material are generally

present in a weight ratio of **tramadol** material to opioid material of from about 200:1 to 1:20. This ratio varies within the disclosed range depending upon the. . . ratios within this range will result in a composition which exhibits synergistic analgesic effects. For example, in a composition comprising **tramadol** and codeine the ratio of the components is from about 20:1 to 1:20, preferably from about 2:1 to 1:2, and, more preferably, from about 2:1 to 1:1. In a composition comprising **tramadol** and oxycodone, the ratio of the components is from about 200:1 to 1:1; more preferably from about 20:1 to about. . .

DETD Pharmaceutical compositions comprising the **tramadol** material and any of codeine, oxycodone or hydrocodone as the active ingredients in intimate admixture with a pharmaceutical carrier can. . .

DETD Preparation of the Combined Doses of **Tramadol** and Codeine

DETD . . . having a concentration expressed in mg.sub.drug(s) per 5 mL of distilled water. For example, in the case of the 1:20 **tramadol** :codeine ratio, 9.1 mg of **tramadol** hydrochloride (=8.0 mg of **tramadol** as the base) and 217.1 mg of codeine phosphate (=160.0 mg of codeine as the free base) were each dissolved. . . combined to prepare the final desired drug combination per 10 mL of distilled water. For example, 5 mL of the **tramadol** stock solution was combined with 5 mL of the codeine stock solution to yield the 1:20 dose, (i.e., 8 mg **tramadol**:160 mg codeine) in 10 mL of water. Then 10 mL/kg of the stock solution was injected into the mouse. See,. . .

DETD Preparation of the Combined Doses of **Tramadol** and Oxycodone

DETD The preparation of different ratios of a **tramadol**/oxycodone combination is effected by preparing a stock solution having a concentration expressed in mg.sub.drugs per 10 mL of dissolved water. For example, 80 mg of **tramadol** as the free base and 4 mg of oxycodone as the free base are dissolved in 10 mL of water to yield the stock solution of (80 mg:4 mg) **tramadol**/oxycodone combination per 10 mL of water. The stock solution of the drug combination is then diluted with a sufficient amount. . . . lower doses of the drug combination per 10 mL of dissolved water. For example, 5 mL of the stock 20:1 **tramadol**/oxycodone combination are diluted with an equal volume of distilled water to yield the lower 20:1 dose, i.e., (40 mg:2 mg),. . .

DETD Preparation of the Combined Doses of **Tramadol** and Hydrocodone

DETD The preparation of different ratios of a **tramadol**/hydrocodone combination is effected by preparing a stock solution having a concentration expressed in mg.sub.drugs per 10 mL of dissolved water. For example, 160 mg of **tramadol** as the free base and 160 mg of hydrocodone as the free base are dissolved in 10 mL of water to yield the stock solution of (160 mg:160 mg) **tramadol**/hydrocodone combination per 10 mL of water. The stock solution of the drug combination is then diluted with a sufficient amount. . . lower doses of the drug combination per 10 mL of dissolved water. For example, 5 mL of the stock 1:1 **tramadol**/hydrocodone combination are diluted with an equal volume of distilled water to yield the lower 1:1 dose, (i.e., 80 mg:80 mg). . .

DETD **Tramadol** N-oxide: Its Synthesis and the Preparation of Doses of **Tramadol** N-oxide with an Opioid

DETD First, **tramadol** N-oxide was prepared as set forth hereinafter. **Tramadol** hydrochloride (0.5 mol) was converted its free base in basified water (pH >9) and then extracted with ether. The ether was evaporated to yield the crystalline hydrate of **tramadol.** The solid was then heated with steam under a high vacuum to remove as much water as possible to yield. . . The solid was collected by filtration, washed with ethyl acetate and dried in vacuo to yield 126.6 g of the **tramadol** N-oxide (mp. 159.5°-160° C.).

DETD The preparation of different ratios of a **tramadol** N-oxide/opioid combination is effected by preparing a stock solution that corresponds to the highest dose of a particular ratio of the

tramadol N-oxide/opioid combination having a concentration expressed in mg.sub.drugs per 10 mL of distilled water. For example, 160 mg of **tramadol** N-oxide as the free base and 160 mg of the opiate oxycodone as the free base are dissolved in 10 mL of distilled water to yield the highest dose of the 1:1 (160 mg:160 mg) **tramadol** N-oxide/oxycodone combination per 10 mL of water. The stock solution of the drug combination is then diluted with a sufficient. . . lower doses of the drug combination per 10 mL of dissolved water. For example, 5 mL of the stock 1:1 **tramadol** N-oxide/oxycodone combination are diluted with an equal volume of distilled water to yield the lower 1:1 dose (i.e., 80 mg:80. . .

DETD (-) and (+) Enantiomers of O-Desmethyl **Tramadol**: Their Syntheses and the Preparation of Doses of O-Desmethyl **Tramadol** with an Opioid

DETD First, O-desmethyl **tramadol** was prepared as set forth hereinafter. Diethylene glycol (125 mL) was added with cooling to potassium hydride (9.5 g) with. . . maintained at <50° C. To the solution was added thiophenol (10 mL) dissolved in diethylene glycol (25 mL), and then (-)-**tramadol** as the free base (9.3 g) in diethylene glycol (50 mL) was added. The final reaction mixture was heated slowly. . . was recrystallized from ethanol/ethyl ether and dried to yield 1.80 g of the salt of the (-) enantiomer of O-desmethylated **tramadol** (mp. 242°-3° C.), [α].sub.D.sup.25 =-32.9 (C=1, EtOH).

DETD To prepare the (+) enantiomer of the title compound, the reaction was run under the same conditions except that (+)-**tramadol** as the free base was used instead of the (-)-**tramadol** to yield 2.8 g of the (+) enantiomer of O-desmethyl **tramadol** (mp. 242°-3° C.) [α].sub.D.sup.25 =+32.2 (C=1, EtOH).

DETD The preparation of different ratios of O-desmethyl **tramadol** /opioid combinations is effected by preparing a stock solution that corresponds to the highest dose of a particular ratio of the O-desmethyl **tramadol**/opioid combination having a concentration expressed in mg.sub.drugs per 10 mL of distilled water. For example, 160 mg of O-desmethyl **tramadol** as the free base and 80 mg of the opiate hydrocodone as the free base are dissolved in 10 mL of distilled water to yield the highest dose of a 2:1 (160 mg:80 mg) O-desmethyl **tramadol**/hydrocodone combination per 10 mL of water. The stock solution of the drug combination is then diluted with a sufficient amount. . . lower doses of the drug combination per 10 mL of distilled water. For example, 5 mL of the stock 2:1 **tramadol** O-desmethyl/hydrocodone combination are diluted with an equal volume of distilled water to yield a lower 2:1 dose (i.e., 80 mg:40. . .

DETD . . . two drugs under additivity. ED50.sub.mix was then compared to ED50.sub.add via a t-test. The ED50 value (95% confidence interval) for **tramadol** hydrochloride alone was 76.8 (59.2-99.7) mg/kg. The ED50 value (and 95% confidence interval) for codeine phosphate alone was 71.3 (52.0-97.7). . .

DETD The interaction between **tramadol** and codeine or hydrocodone were determined at precise dosage ratios of **tramadol** hydrochloride and codeine or oxycodone. Multiple (typically 4-6) coded doses of each selected combination were studied for analgesic effectiveness after. . .

DETD The interaction of **tramadol** hydrochloride and codeine phosphate or oxycodone sulfate on tail-flick latency in mice was demonstrated by the data in Tables I. . . indicate superadditivity, i.e., unexpected enhancement of effects. The diagonal dashed lines radiating from the origin represent the dose ratios of **tramadol** hydrochloride to codeine phosphate (FIG. 1) or oxycodone sulfate (FIG. 2) used in mice receiving the combined drug dosages. The bars through the ED50 points for **tramadol** and codeine or oxycodone compositions represent the 95% confidence intervals of the ED50.

DETD The experimental data as represented in FIG. I establishes that

compositions having a ratio of **tramadol** to codeine from 1:20 to 20:1 (represented by the curved line) give unexpectedly enhanced activity since ED50.sub.mix is less than ED50.sub.add. The experimental data as represented in FIG. II similarly establishes that .compositions having a ratio of **tramadol** to oxycodone from 200:1 to 1:1 also give unexpectedly enhanced activity. Furthermore, the use of hydrocodone in a composition of. . .

DETD TABLE I

TRAMADOL:CODEINE

DRUG COMBINATION (**Tramadol**:Codeine)	DOSE (mg/kg, p.o.) **Tramadol**	Codeine	Analgesia	ED.sub.50 at 15 min (95% Cl's) **Tramadol**	Codeine
tramadol only	20	0	0/10		
	40	0	1/10		
	80	0	4/10	76.8	--
	160	0	9/10	(59.2-99.7)	
	200	0	10/10		
20:1	20.	.	.		

DETD TABLE II

TRAMADOL:OXYCODONE

DRUG COMBINATION (**Tramadol**:Codeine)	DOSE (mg/kg, p.o.) **Tramadol**	Codeine	Analgesia	ED.sub.50 at 15 min (95% Cl's) **Tramadol**	Oxycodone
tramadol only	20	0	0/10		
	40	0	2/10		
	80	0	4/10	76.8	--
	160	0	9/10	(59.2-99.7)	
	200	0	10/10		
200:1	20.	.	.		

CLM What is claimed is:

1. A pharmaceutical composition comprising a **tramadol** material selected from the group consisting of **tramadol**, its stereoisomers and its pharmaceutically acceptable salts and an opioid selected from the group consisting of codeine and oxycodone, wherein the weight ratio of the **tramadol** material to the opioid is of from about 1:20 to about 20:1.

3. The pharmaceutical composition of claim 2 wherein the **tramadol** material is **tramadol** hydrochloride.

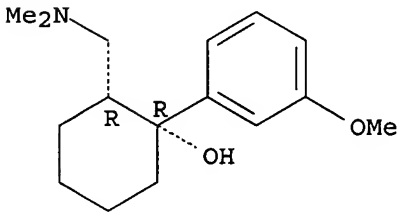
4. The pharmaceutical composition of claim 3 wherein the **tramadol** hydrochloride is racemic.

8. The pharmaceutical composition of claim 7 wherein said **tramadol** material is **tramadol** hydrochloride.

9. The pharmaceutical composition of claim 8 wherein the **tramadol** hydrochloride is racemic.

IT **36282-47-0**, Tramadol hydrochloride
(conversion of, to hydrate)
IT **27203-92-5**
(oxidation of)
IT **144830-14-8P**, (+)-O-Desmethyltramadol **147441-56-3P**, Tramadol N-oxide **148218-19-3P**, (-)-O-Desmethyltramadol hydrochloride
(preparation of, analgesic compns. containing)
IT **36282-47-0**, Tramadol hydrochloride
(conversion of, to hydrate)
RN 36282-47-0 USPATFULL
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

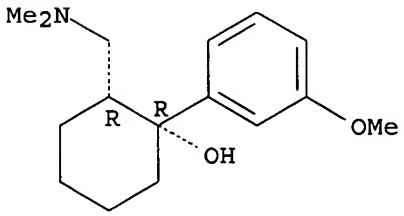
Relative stereochemistry.



● HCl

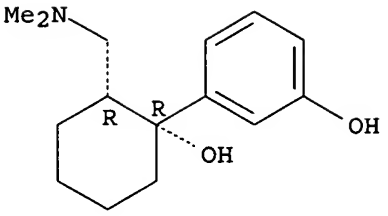
IT **27203-92-5**
(oxidation of)
RN 27203-92-5 USPATFULL
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



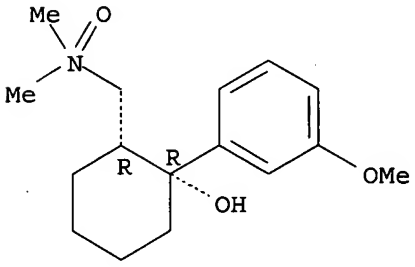
IT **144830-14-8P**, (+)-O-Desmethyltramadol **147441-56-3P**, Tramadol N-oxide **148218-19-3P**, (-)-O-Desmethyltramadol hydrochloride
(preparation of, analgesic compns. containing)
RN 144830-14-8 USPATFULL
CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



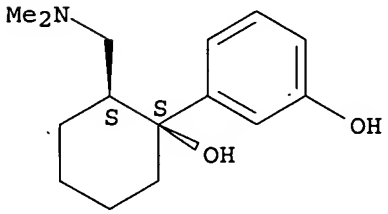
RN 147441-56-3 USPATFULL
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 148218-19-3 USPATFULL
CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

L117 ANSWER 5 OF 10 USPATFULL on STN
AN 94:68779 USPATFULL
TI Composition comprising a **tramadol** material and **acetaminophen** and its use
IN **Raffa, Robert B.**, Norristown, PA, United States
Vaught, Jeffrey L., Perkosie, PA, United States
PA McNeilab, Inc., Spring House, PA, United States (U.S. corporation)
PI US 5336691 19940809
AI US 1992-974865 19921110 (7)
RLI Continuation-in-part of Ser. No. US 1991-755924, filed on 6 Sep 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Waddell, Frederick E.; Assistant Examiner: Jarvis,

William R. A.
LREP Palo, Ralph R.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 555
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a composition comprising a **tramadol** material and **acetaminophen**, and its use. As used herein **tramadol** refers to various forms of **tramadol.** The compositions are pharmacologically useful in treating pain and tussive conditions. The compositions are also subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compositions are within certain ratios the pharmacological effects of the compositions are superadditive (synergistic).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Composition comprising a **tramadol** material and **acetaminophen** and its use
IN **Raffa, Robert B.**, Norristown, PA, United States
IN **Vaught, Jeffrey L.**, Perkosie, PA, United States
AB This invention relates to a composition comprising a **tramadol** material and **acetaminophen**, and its use. As used herein **tramadol** refers to various forms of **tramadol.** The compositions are pharmacologically useful in treating pain and tussive conditions. The compositions are also subject to less opioid side-effects. . .
SUMM . . . analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1RS, 2RS)-[(dimethylamino)-methyl]-1-(3-methoxyphenyl)cyclohexanol, commonly known as **tramadol**, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of **tramadol** are found in Arzneim. Forsch, (Drug Res.), 28(I), 114 (1978). Driessen et al., Arch. Pharmacol., 341, R104 (1990) disclose that **tramadol** produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the VI th World Congress on Pain, Apr. 1-6 (1990), disclose that **tramadol** hydrochloride is an orally active pure agonist opioid analgesic. However, clinical experience indicates that **tramadol** lacks many of the typical side effects of opioid agonists, e.g., respiratory depression (W. Vogel et al., Arzneim. Forsch. (Drug. . . Yanagita, Arzneim. Forsch, (Drug Res.), 28(I), 158 (1978)). When given at a dose of 50 mg by rapid i.v. injection, **tramadol** may produce certain side effects unique to **tramadol** including hot flushes and sweating. Despite these side effects, **tramadol**'s combination of non-opioid and opioid activity makes **tramadol** a very unique drug. **Tramadol** is currently being marketed by Grunenthal GMBH as an analgesic.
SUMM As alternatives to using opioids, non-opioids such as **acetaminophen** (APAP) and aspirin are used as analgesics. APAP, like aspirin, is not subject to the tolerance, addiction and toxicity of. . .
SUMM . . . al., Arch. Int. Pharmacodyn., 235, 116 (1978) report superadditive analgesia with a 1:125 mixture of butorphanol, another opioid analgesic, and **acetaminophen** (APAP), a non-opioid analgesic, whereas a 1:10 mixture did not show any statistically significant superadditive analgesia.
SUMM The prior art, however, does not disclose that **tramadol** an `atypical` opioid analgesic, can or should be combined with another analgesic to lessen the side effects of each or to yield a composition comprising a **tramadol** material and another analgesic that exhibits superadditive analgesia.

SUMM It has now been found that a **tramadol** material which includes various forms of **tramadol** as defined hereinafter can be combined with APAP to produce analgesia. The combination employs lesser amounts of both the **tramadol** material and APAP than would be necessary to produce the same amount of analgesia if either was used alone. By. . . of both drugs the side effects associated with each are reduced in number and degree. Surprisingly, the compositions comprising the **tramadol** material and APAP have been found to exhibit synergistic analgesic effects when combined in certain ratios. The compositions according to. . .

DRWD FIG. 1 is an isobologram showing the analgesic effect of **tramadol** hydrochloride and **acetaminophen** composition on the acetylcholine-induced abdominal constriction in mice.

DETD The present invention is directed to compositions comprising a **tramadol** material and **acetaminophen.** The **tramadol** material is any one of (1R, 2R or 1S, 2S)-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol (**tramadol**), its N-oxide derivative ("**tramadol** N-oxide"), and its O-desmethyl derivative ("O-desmethyl **tramadol** ") or mixtures thereof. It also includes the individual stereoisomers, mixtures of stereoisomers, including the racemates, pharmaceutically acceptable salts of the amines, such as the hydrochloride salt, solvates and polymorphs of the **tramadol** material. **Tramadol** is commercially available from Grunenthal or may be made by the process described in U.S. Pat. No. 3,652,589, which is. . .

DETD **Tramadol** N-oxide is prepared by treating **tramadol** as a free base with an oxidizing agent, e.g., hydrogen peroxide (30%), in an organic solvent, e.g., methanol or isopropanol,. . .

DETD O-Desmethyl **tramadol** is prepared by treating **tramadol** as a free base under O-desmethylating reaction conditions, e.g., reacting it with a strong base such as NaH or KH,. . .

DETD The pharmacology of **acetaminophen** is reviewed by B. Ameer et al., Ann. Int. Med., 87, 202 (1977), and the preparation of **acetaminophen** is disclosed in U.S. Pat. No. 2,998,450, which is incorporated herein by reference.

DETD The APAP and the **tramadol** material are generally present in a weight ratio of **tramadol** material to APAP from about 1:1 to 1:1600. Certain ratios result in a composition which exhibits synergistic analgesic effects. For example, in a composition comprising a **tramadol** material and APAP, the ratio of the **tramadol** material: APAP is preferably from about 1:5 to 1:1600; and, more preferably, from about 1:19 to 1:800.

DETD The most preferred ratios are from about 1:19 to 1:50. Compositions of a **tramadol** material and APAP within these weight ratios have been shown to exhibit synergistic analgesic effects. In addition, the particular compositions. . .

DETD The **tramadol**/APAP formulations according to the present invention may also contain therapeutically effective amounts of one or more other pharmaceutical actives including. . . pharmaceutically acceptable salts thereof) and combinations of any of the aforesaid pharmaceuticals. The aforesaid pharmaceuticals may be combined with a **tramadol/acetaminophen** formulation for the treatment of such ailments as allergies, sleep disorders, cough, colds, cold-like and/or flu symptoms in mammals including. . .

DETD Pharmaceutical compositions comprising the **tramadol** material and **acetaminophen** and when desired other pharmaceutical actives in an intimate admixture with a pharmaceutical carrier can be prepared according to conventional. . . amounts of active components being used. In the case wherein one or more other pharmaceutical components are added to the **tramadol**/APAP composition those components may be added in amounts known in the art and may be given at dosages conventional for. . .

DETD Preparation of the Combined Doses of **Tramadol** and APAP

DETD The preparation of different ratios of a **tramadol**/APAP combination is effected by first preparing a stock solution of **tramadol** having a concentration expressed in mg.sub.drugs per 10 mL of distilled water. For example, 8 mg of **tramadol** as the free base is dissolved per 10 mL of water to yield the highest dose of **tramadol** stock solution. The stock solution of the **tramadol** is then diluted with a sufficient amount of distilled water to prepare the lower doses of the **tramadol** per 10 mL of distilled water. The combinations are then made by adding 10 mL of each dilution to the appropriate mg of APAP to achieve the desired ratio of **tramadol** to APAP. For the 1:50 example: 400 mg of APAP as the free base is suspended with 10 mL of the 8 mg **tramadol** solution and 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the 1:50 ratio,. .

.

DETD Preparation of the Combined Doses of **Tramadol** N-oxide and APAP

DETD First, **tramadol** N-oxide was prepared as set forth hereinafter. **Tramadol** hydrochloride (0.5 mol) was converted to its free base in basified water (pH >9) and then extracted with ether. The ether was evaporated to yield the crystalline hydrate of **tramadol.** The solid was then heated with steam under a high vacuum to remove as much water as possible to yield. . . The solid was collected by filtration, washed with ethyl acetate and dried in vacuo to yield 126.6 g of the **tramadol** N-oxide (mp. 159.5°-160° C.).

DETD The preparation of different ratios of a **tramadol** N-oxide/APAP combination is effected by first preparing a stock solution of **tramadol**-N-oxide having a concentration expressed in mg.sub.drugs per 10 mL of distilled water. For example, 8 mg of **tramadol** N-oxide as the free base is dissolved per 10 mL of water to yield the highest dose of **tramadol** stock solution. The stock solution of the **tramadol**-N-oxide is then diluted with a sufficient amount of distilled water to prepare the lower doses of the **tramadol** N-oxide per 10 mL of distilled water. The combinations are then made by adding 10 mL of each dilution to the appropriate mg of APAP to achieve the desired ratio of **tramadol** N-oxide to APAP. For the 1:50 example: 400 mg of APAP as the free base is suspended with 10 mL of the 8 mg **tramadol** N-oxide solution and 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the 1:50. . .

DETD (-) and (+) Enantiomers of O-Desmethyl **Tramadol**: Their Syntheses and the Preparation of Doses of O-Desmethyl **Tramadol** -with APAP

DETD First, O-desmethyl **tramadol** was prepared as set forth hereinafter. Diethylene glycol(125 mL) was added with cooling to potassium hydride (9.5 g) with the. . . maintained at <50° C. To the solution was added thiophenol (10 mL) dissolved in diethylene glycol (25 mL), and then (-)-**tramadol** as the free base (9.3 g) in diethylene glycol (50 mL) was added. The final reaction mixture was heated slowly. . . was recrystallized from ethanol/ethyl ether and dried to yield 1.80 g of the salt of the (-) enantiomer of O-desmethyl **tramadol** (mp. 242°-3° C.), [α].sub.D.sup.25 =-32.9 (C=1, EtOH).

DETD To prepare the (+) enantiomer of the title compound, the reaction was run under the same conditions except that (+)-**tramadol** as the free base was used instead of the (-)-**tramadol** to yield 2.8 g of the (+) enantiomer of O-desmethyl **tramadol** (mp. 242°-3° C.) [α].sub.D.sup.25 =+32.2 (C=1, EtOH).

DETD The preparation of different ratios of a O-desmethyl/APAP combination is effected by first preparing a stock solution of O-desmethyl **tramadol** having a concentration expressed in mg.sub.drugs per 10 mL of distilled water. For example, 8 mg of O-desmethyl **tramadol** as the free base is dissolved per 10 mL of water to yield the highest dose of O-desmethyl **tramadol** stock solution. The stock

solution of the O-desmethyl **tramadol** is then diluted with a sufficient amount of distilled water to prepare the lower doses of the O-desmethyl **tramadol** per 10 mL of distilled water. The combinations are then made by adding 10 mL of each dilution to the appropriate mg of APAP to achieve the desired ratio of O-desmethyl **tramadol** to APAP. For the 1:50 example: 400 mg of APAP as the free base is suspended with 10 mL of the 8 mg O-desmethyl **tramadol** solution and 2 drops of TWEEN 80, a pharmacological dispersant, manufactured by Fisher Scientific Company, to yield the 1:50 ratio,. . .

DETD . . . utilized in determining the analgesic effects associated with the compositions of the invention. The mice were all dosed orally with **tramadol** hydrochloride (calculated as the base), which was completely dissolved in distilled water, and **acetaminophen** (calculated as the base), which was completely dissolved in distilled water or in distilled water containing 2% by volume of. . .

DETD Mice, intubated with various doses of **tramadol** hydrochloride alone, **acetaminophen** alone, combined doses of **tramadol** hydrochloride and **acetaminophen**, or vehicle such as distilled water, or distilled water containing 2% by volume of Tween 80, were injected intraperitoneally with. . . abdominal constriction response beginning immediately after receiving the acetylcholine dose, which was 30 minutes after receiving the oral administration of **tramadol** hydrochloride, **acetaminophen**, combined doses of **tramadol** hydrochloride and **acetaminophen**, or vehicle. Each mouse was used only once.

DETD . . . for the two drugs under additivity. ED50.sub.mix was then compared to ED50.sub.add via a Student's t-test. The ED50 value for **tramadol** hydrochloride alone was 5.5(4.8-6.4) mg/kg. The ED50 value for **acetaminophen** alone was 164.3 (122.7-219.9) mg/kg.

DETD The interaction between **tramadol** and **acetaminophen** was determined at precise dosage ratios of **tramadol** hydrochloride and **acetaminophen.** Multiple (typically 4-6) coded doses of each selected combination were studied for analgesic effectiveness after 30 minutes using an experimental. . .

DETD The interaction of **tramadol** hydrochloride and **acetaminophen** on the acetylcholine-induced abdominal constriction in mice was demonstrated by the data in Table I and is shown in the. . . i.e., unexpected enhancement of effects. The diagonal dashed lines radiating from the origin represent the dose ratios of APAP to **tramadol** hydrochloride used in mice receiving the combined drug dosages. The bars through the ED50 points for the **tramadol** and APAP composition represent the 95% confidence intervals of the ED50 value. The experimental data as represented in FIG. I establishes that compositions having a ratio of **tramadol** to APAP from 1:1 to 1:1600 (represented by the curved line) give unexpectedly enhanced activity since ED50.sub.mix is less than. . .

DETD TABLE I

TRAMADOL:APAP DRUG COMBINATIONS (**Tramadol**:APAP)	DOSE (mg/kg, p.o.) **Tramadol**	APAP	ED.sub.50 30 min (95% CI's) analgesia **Tramadol** APAP
tramadol only	2	0	3/15
	3	0	4/15
	4	0	14/45

6 0 20/45
5.5
8 0 40/60
(4.8-6.4)
10 0. . .

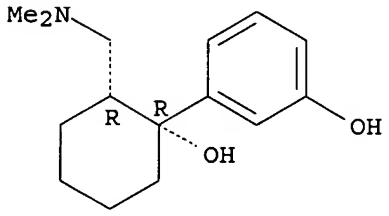
CLM What is claimed is:
1. A pharmaceutical composition comprising a **tramadol** material and **acetaminophen**, wherein the ratio of the **tramadol** material to **acetaminophen** is a weight ratio from about 1:1 to about 1:1600.

2. The pharmaceutical composition of claim 1 wherein the **tramadol** material is **tramadol** hydrochloride.

3. The pharmaceutical composition of claim 2 wherein the **tramadol** hydrochloride is racemic.

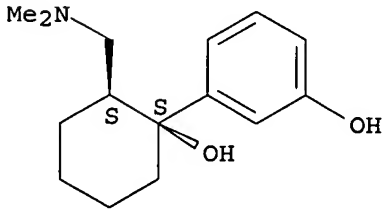
IT **144830-14-8P 144830-15-9P**
(analgesic acetaminophen-tramadol compns.)
IT **103-90-2**, Acetaminophen **27203-92-5**, Tramadol
36282-47-0, Tramadol hydrochloride **147441-56-3**,
Tramadol N-oxide
(analgesic acetaminophen-tramadol compns.)
IT **148229-78-1**, (+)-Tramadol **148229-79-2**, (-)-Tramadol
(analgesic acetaminophen-tramadol compns.)
IT **148218-19-3P**
(analgesic acetaminophen-tramadol compns.)
IT **144830-14-8P 144830-15-9P**
(analgesic acetaminophen-tramadol compns.)
RN 144830-14-8 USPATFULL
CN Phenol, 3-[(1R,2R)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



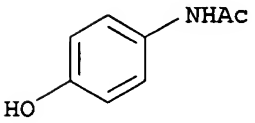
RN 144830-15-9 USPATFULL
CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



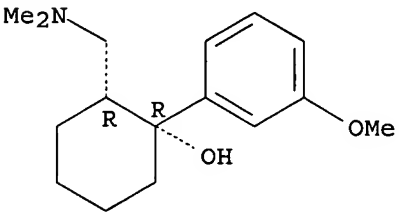
IT **103-90-2**, Acetaminophen **27203-92-5**, Tramadol
36282-47-0, Tramadol hydrochloride **147441-56-3**,

Tramadol N-oxide
(analgesic acetaminophen-tramadol compns.)
RN 103-90-2 USPATFULL
CN Acetamide, N-(4-hydroxyphenyl)- (9CI) (CA INDEX NAME)



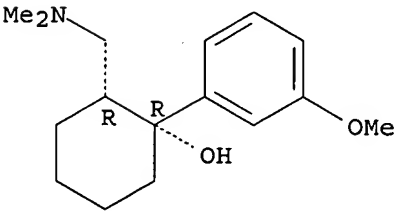
RN 27203-92-5 USPATFULL
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 36282-47-0 USPATFULL
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

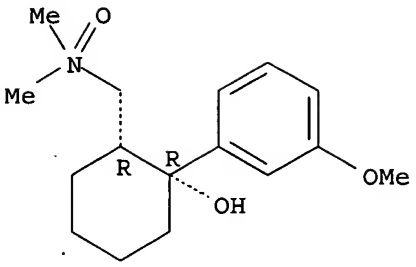
Relative stereochemistry.



● HCl

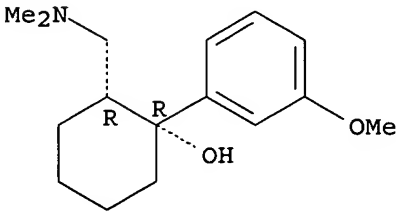
RN 147441-56-3 USPATFULL
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **148229-78-1**, (+)-Tramadol **148229-79-2**, (-)-Tramadol
(analgesic acetaminophen-tramadol compns.)
RN 148229-78-1 USPATFULL
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)- (9CI) (CA INDEX NAME)

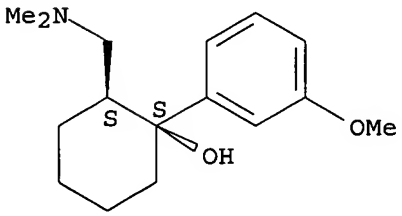
Absolute stereochemistry. Rotation (+).



● HCl

RN 148229-79-2 USPATFULL
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1S,2S)- (9CI) (CA INDEX NAME)

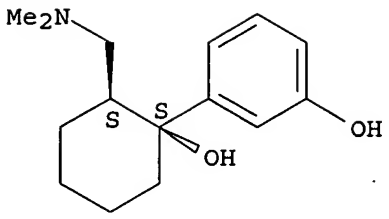
Absolute stereochemistry. Rotation (-).



● HCl

IT **148218-19-3P**
(analgesic acetaminophen-tramadol compns.)
RN 148218-19-3 USPATFULL
CN Phenol, 3-[(1S,2S)-2-[(dimethylamino)methyl]-1-hydroxycyclohexyl]-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

L117 ANSWER 6 OF 10 USPATFULL on STN
AN 93:52619 USPATFULL
TI **Tramadol** N-oxide material, enantiomers and compositions thereof, and their use
IN Maryanoff, Cynthia A., New Hope, PA, United States
Raffa, Robert B., Norristown, PA, United States
Villani, Frank J., Perkasie, PA, United States
PA McNeilab, Inc., Spring House, PA, United States (U.S. corporation)
PI US 5223541 19930629
AI US 1991-759259 19910913 (7)
DT Utility
FS Granted
EXNAM Primary Examiner: Raymond, Richard L.; Assistant Examiner: O'Sullivan, P.
LREP Palo, Ralph R.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 249
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a **tramadol** N-oxide material, enantiomers and compositions thereof and their use. The **tramadol** N-oxide material and compositions thereof are pharmacologically useful in treating pain, diarrhea and tussive conditions. The **tramadol** N-oxide is also subject to less side-effects as compared to pure opiate based compositions, such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, the **tramadol** N-oxide material when administered orally exhibits analgesia for a longer duration than an equi-analgesic amount of **tramadol.**

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Tramadol** N-oxide material, enantiomers and compositions thereof, and their use
IN **Raffa, Robert B.**, Norristown, PA, United States
AB This invention relates to a **tramadol** N-oxide material, enantiomers and compositions thereof and their use. The **tramadol** N-oxide material and compositions thereof are pharmacologically useful in treating pain, diarrhea and tussive conditions. The **tramadol** N-oxide is also subject to less side-effects as compared to pure opiate based compositions, such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, the **tramadol** N-oxide material when administered orally exhibits analgesia for a longer duration than an equi-analgesic amount of **tramadol.**
SUMM . . . discloses a class of analgesic cycloalkanol-substituted phenol esters having a basic amine group in the cycloalkyl ring. The compound (1RS, 2RS)-**2-[(dimethylamino)-methyl]-1-(3-methoxyphenyl)cyclohexanol,**

commonly known as **tramadol**, is specifically disclosed therein. A series of articles pertaining to the pharmacology, toxicology and clinical studies of **tramadol** are found in Arzneim. Forsch. (Drug Res.), 28(I), 114 (1978). Driessen et al., Arch. Pharmacol., 341, R104 (1990) disclose that **tramadol** produces its analgesic effect through a mechanism that is neither fully opioid-like nor non-opioid-like. The Abstracts of the VIth World Congress on Pain, Apr. 1-6 (1990) disclose that **tramadol** hydrochloride is an orally active pure opioid agonist analgesic. However, clinical experience indicates that **tramadol** lacks many of the typical side effects of opioid agonists, e.g., respiratory depression (W. Vogel et al., Arzneim. Forsch. (Drug. . . Yanagita, Arzneim. Forsch. (Drug Res.), 28(I), 158 (1978)). When given at a dose of 50 mg by rapid I.V. injection, **tramadol** may, however, produce certain side effects unique to **tramadol** including hot flashes and sweating. Another disadvantage to the use of **tramadol** is that it is an immediate acting drug and thus must be taken a number of times over a 24 hour period to sustain analgesia. Despite these disadvantages, **tramadol**'s combination of non-opioid and opioid activity makes **tramadol** a very unique drug. **Tramadol** is currently being marketed by Grunenthal GMBH in Germany as an analgesic.

SUMM . . . assess the pharmacological activity of the derivatives. Flick et al., Arzneim, Forsch., 28, 107 (1978), disclose that the only desmethyl **tramadol** that exhibits analgesia is the O-desmethyl **tramadol**, and the reference also discloses that the O-desmethyl **tramadol** is analgesically more effective than **tramadol** . B. Klentey et al., Arzneim. Forsch., 7, 594 (1957) disclose that the N-oxides of dihydromorphinone, morphinone and dihydrohydroxycodeinone do not. . .

SUMM The prior art, therefore, does not disclose or suggest an N-oxide of a **tramadol** material or that the N-oxide of a **tramadol** material would exhibit an analgesic effect or would exhibit a pharmacological effect having a longer duration, e.g., of analgesia, than its corresponding non-N-oxide, e.g., **tramadol.**

SUMM Accordingly, the present invention is directed to a **tramadol** N-oxide material having the following formula I: ##STR1## enantiomers and compositions thereof and their use. The **tramadol** N-oxide material and compositions thereof are pharmacologically useful in treating pain, diarrhea and tussive conditions. The **tramadol** N-oxide material is also subject to less side-effects as compared to a pure opioid or opiate based compositions, such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, **tramadol** N-oxide when administered orally exhibits analgesia for a longer duration than an equi-analgesic amount of **tramadol.** As defined herein longer duration means for more than 2 hours and preferably for 4 to up to at least. . .

DRWD FIG. 1 is a graph showing the % of analgesia effected versus the dose of **tramadol** and **tramadol** N-oxide ascertained by the abdominal constriction test in mice; and

DRWD FIG. 2 is a bar graph showing time course of the % of analgesia effected by **tramadol** N-oxide versus **tramadol** hydrochloride at equianalgesic doses ascertained by the abdominal constriction test in mice.

DETD More particularly, the **tramadol** N-oxide material according to the present invention is either of the N-oxide derivative of (1R, 2R or 1S, 2S)-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol-N-oxide ("**tramadol** N-oxide") or mixtures thereof. It also includes the individual stereoisomers, such as those of formulas II & III: ##STR2## and. . .

DETD **Tramadol** N-oxide is prepared by treating **tramadol** (commercially available from Grunenthal or may be made by the process described in U.S. Pat. No. 3,652,589, which is herein. . .

DETD The **tramadol** N-oxide material may be used alone or be combined

with other active ingredients such as analgesic agents including **acetaminophen**, codeine, oxycodone, hydrocodone and ibuprofen. This ratio of the **tramadol** N-oxide material and the other active ingredient will vary depending upon the particular components of the composition.

DETD Pharmaceutical compositions comprising the **tramadol** N-oxide material alone or in combination with one or more other active ingredients in an intimate admixture with a pharmaceutical. . .

DETD Example 1: **Tramadol** N-oxide

DETD **Tramadol** N-oxide was prepared as set forth hereinafter. **Tramadol** hydrochloride (0.5 mol) was converted its free base in basified water (pH>9) and then extracted with ether. The solid was. . . The solid was collected by filtration, washed with ethyl acetate and dried in vacuo to yield 126.6 g of the **tramadol** N-oxide (mp. 159.5°-160° C.).

DETD . . . utilized in determining the analgesic effects associated with the compositions of the invention. The mice were all dosed orally with **tramadol** hydrochloride or **tramadol** N-oxide (calculated as the base),

DETD Mice, intubated with various doses of **tramadol** hydrochloride or **tramadol** N-oxide were injected intraperitoneally with a challenge dose of acetylcholine bromide. The acetylcholine was completely dissolved in distilled water; the. . . abdominal constriction response beginning immediately after receiving the acetylcholine dose, which was 30 minutes after receiving the oral administration of **tramadol** hydrochloride or **tramadol** N-oxide. Each mouse was used only once.

DETD . . . the dose of each compound which produced an equal level (90%) of analgesia (the ED90 dose). Th ED90 dose of **tramadol** hydrochloride was estimated to be 12 mg/kg p.o. (See, FIG. 1) and the ED90 dose of **tramadol** N-oxide was estimated to be 40 mg/kg p.o. (See, FIG. 1). The respective ED90 doses of both compounds were then. . . of mice at various times prior to the challenge by acetylcholine as described above. Separate groups of mice received either **tramadol** or **tramadol** N-oxide at 15, 30, 60, 120, 180, 240 or 300 minutes prior to the acetylcholine challenge. The percentage of analgesia. . . response according to equation {1}. The duration of analgesic effect (determined as the time percentage analgesia dropped below 50%) of **tramadol** was between 60 and 120 minutes (See, FIG. 2), whereas the duration of analgesic effect for **tramadol** N-oxide was between 240 and 300 minutes. The greater duration of analgesic action of **tramadol** N-oxide at equi-analgesic doses to **tramadol** also demonstrates that for doses of equal duration, requiring raising the dose of **tramadol**, the level of **tramadol** required would be greater than the therpeutically prudent dose and, thus, would likely represent an unacceptable increase in the side effects, and hence, decrease in safety margin of **tramadol**.

IT **36282-47-0**, Tramadol hydrochloride
(oxidation of, in pharmaceutical preparation)

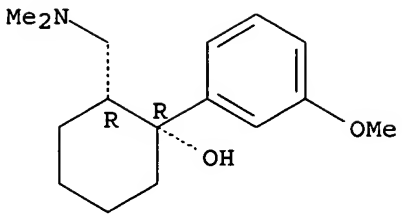
IT **147441-56-3P**
(preparation of, for treatment of pain and diarrhea and tussive conditions)

IT **36282-47-0**, Tramadol hydrochloride
(oxidation of, in pharmaceutical preparation)

RN 36282-47-0 USPATFULL

CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, hydrochloride, (1R,2R)-rel- (9CI) (CA INDEX NAME)

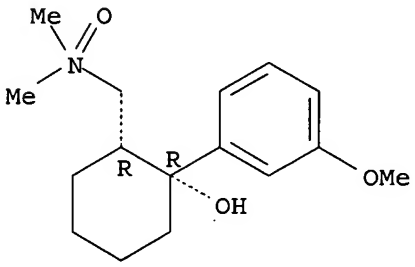
Relative stereochemistry.



● HCl

IT **147441-56-3P**
(preparation of, for treatment of pain and diarrhea and tussive conditions)
RN 147441-56-3 USPATFULL
CN Cyclohexanol, 2-[(dimethyloxidoamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L117 ANSWER 7 OF 10 USPATFULL on STN
AN 93:31188 USPATFULL
TI External preparation comprising calcium silicate
IN Shiobara, Takao, 20-18, Keyaki 1-chome, Honjo-shi, Saitama, Japan
Nonaka, Jun, 15-4, Midori 1-chome, Honjo-shi, Saitama, Japan
Kasai, Masayoshi, 156, Tsutsujigaoka 5-chome, Kakamigahara-shi, Gifu, Japan
Konita, Takeshi, 2-2, Fukiagemachihoncho 3-chome, Kitaadachi-gun, Saitama, Japan
PI US 5204119 19930420
AI US 1991-748208 19910820 (7) <--
PRAI JP 1990-228669 19900829 <--
DT Utility
FS Granted
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Spear, James M.
LREP Flynn, Thiel, Boutell & Tanis
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 7 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 453
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An external preparation is characterized by comprising calcium silicate. The calcium silicate controls the release rate and percutaneous absorbability of a drug.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AI US 1991-748208 19910820 (7) <--
PRAI JP 1990-228669 19900829 <--

SUMM Indomethacin, ketoprofen, flurbiprofen, **acetaminophen**, alclofenac, perisoxal citrate, sulidanac, sulpyrine, aluminum flufenamate, **tramadol** hydrochloride, sulindac, pentazocine, fentiazac, tolmetin sodium, naproxen, fenbufen, pranoprofen, piroxicam, clofezone, pentazocine, dichlofenac sodium, mepirizole, aspirin, aspirin aluminum, acemetacin, amfenac. . .

L117 ANSWER 8 OF 10 USPATFULL on STN
AN 91:102048 USPATFULL
TI Continuous preparation of solid pharmaceutical forms
IN Klimesch, Roger, Alsbach-Haehnlein, Germany, Federal Republic of
Bleckmann, Gerhard, Lampertheim, Germany, Federal Republic of
Farwerck, Karl-Peter, Worms, Germany, Federal Republic of
Schlemmer, Lothar, Maxdorf, Germany, Federal Republic of
Sanner, Axel, Frankenthal, Germany, Federal Republic of
PA BASF Aktiengesellschaft, Ludwigshafen, Germany, Federal Republic of (non-U.S. corporation)
PI US 5073379 19911217 <--
AI US 1989-398663 19890825 (7) <--
DCD 20060131
PRAI DE 1988-3830353 19880907 <--
DT Utility
FS Granted
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Spear, James M.
LREP Oblon, Spivak, McClelland, Maier & Neustadt
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 813
AB A mixture of one or more pharmaceutical active compounds and one or more thermoplastic polymers is tabletted by a process in which the mixture is extruded and the still moldable extrudate is pressed to give tablets, between two belts, or a belt and a roller, which make contact in parts, rotate in opposite directions and run parallel along the contact zone, the shape-imparting indentations, which may be present in complementary pairs, being located in both or in only one of the revolving shape-imparting elements.

PI US 5073379 19911217 <--
AI US 1989-398663 19890825 (7) <--
PRAI DE 1988-3830353 19880907 <--
SUMM . . . amitriptyline, diclofenac, nifedipine, verapamil, pyritinol, nitrendipine, doxycycline, bromhexin, methylprednisolone, clonidine, fenofibrate, allopurinol, pirenzepine, levothyroxine, tamoxifen, metildigoxin, o-(β-hydroxyethyl)-rutoside, propicillin, acyclovir mononitrate, **paracetamol**, naftidrofuryl, pentoxifylline, propafenone, acebutolol, L-thyroxine, **tramadol**, bromocriptine, loperamide, ketotifen, fenoterol, Ca dobelisate, propranolol, minocycline, nicergoline, ambroxol, metoprolol, β-sitosterine, enalapril hydrogen maleate, bezafibrate, ISDN, gallopamil, xanthinol nicotinate,. . .
SUMM Solid solutions of the following active compounds are particularly preferred: **acetaminophen** (=**paracetamol**), acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β-carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dicumarol, digitoxin,. . .
DETD . . . Benzocaine A 30

30
40 50
60
70
70

10

46 5,5-Diphenhydramine
A 60
80
100
120
120
120
130
10

47 **Paracetamol**
A 60
80
100
120
120
120
130
10

48 Sulfathiazole
A 70
90
100
100
100
100
130
10

49 Vitamin. . .
CLM What is claimed:
. . . 15. A process as claimed in claim 14, wherein one or more active compounds from the following group are used: **acetaminophen** (= **paracetamol**), acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β-carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dircumarol, digitoxin,. .
.

L117 ANSWER 9 OF 10 USPATFULL on STN
AN 89:7426 USPATFULL
TI Preparation of solid pharmaceutical forms
IN Goertz, Hans-Helmut, Freinsheim, Germany, Federal Republic of
Klimesch, Roger G., Alsbach-Haehnlein, Germany, Federal Republic of
Laemmerhirt, Klaus, Boehl-Iggelheim, Germany, Federal Republic of
Lang, Siegfried, Ludwigshafen, Germany, Federal Republic of
Sanner, Axel, Frankenthal, Germany, Federal Republic of
Spengler, Reinhard, Ludwigshafen, Germany, Federal Republic of
PA BASF Aktiengesellschaft, Germany, Federal Republic of (non-U.S. corporation)
PI US 4801460 19890131 <--
AI US 1987-34938 19870406 (7) <--
PRAI DE 1986-3612212 19860411 <--
DT Utility
FS Granted
EXNAM Primary Examiner: Lusignan, Michael
LREP Keil & Weinkauf
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 601
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Process for the preparation of solid pharmaceutical forms by mixing one or more pharmaceutical active compounds with one or more fusible,

pharmacologically tolerated binders and, if required, other conventional pharmaceutical auxiliaries, at from 50° to 180° C., and subjecting the mixture to injection molding or extrusion and shaping, wherein the fusible binder used is a NVP polymer which contains not less than 20% by weight of NVP as copolymerized units, and, where they are present, all of whose comonomers contain nitrogen and/or oxygen.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 4801460 19890131 <--

AI US 1987-34938 19870406 (7) <--

PRAI DE 1986-3612212 19860411 <--

SUMM . . . amitriptylin, diclofenac, nifedipine, verapamil, pyritinol, nitrendipin, doxycycline, bromhexine, methylprednisolone, clonidine, fenofibrate, allopurinol, pirenzepine, levothyroxin, tamoxifen, metildigoxin, o-(β-hydroxyethyl)-rutoside, propicillin, aciclovir mononitrate, **paracetamol**, naftidrofuryl, pentoxifylline, propafenone, acebutolol, L-thyroxin, **tramadol**, bromocriptine, loperamide, ketotifen, fenoterol, cadobelisate, propanolol, enalaprilhydrogen maleate, bezafibrate, ISDN, gallopamil, xantinol nicotinate, digitoxin, flunitrazepam, bencyclane, dexapanthenol, pindolol, lorazepam, diltiazem,. . .

SUMM Solid solutions of the following active compounds are particularly preferred: **acetaminophen** (**paracetamol**), acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β-carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dicoumarol, digitoxin,. . .

DETD . . . Weight ratio

			T1	T2	T3	T4	T5	T6
								°C.
17a	Benzocaine							
	A	1:3	20	30	40	40	50	50
18	**Paracetamol**							50
	C	1:3	60	80	100	120	120	120
19	Phenytoin							120
	C	1:3	60	80	100	120	120	120
20	Benzocaine							120
. . .	Benzocaine							
	C	1:1	30	30	40	50	50	60
28	Phenytoin							60
	A	1:3	60	80				

100
120
120
120
130

29 **Paracetamol**
A 1:3 60
80
100
120
120
120
130

30 Sulfathiazole
A 1:1 70
90
100
100
100
100
130

31 Benzocaine
. . .
CLM What is claimed is:
. . . 7. A process as defined in claim 1, wherein one or more active compounds from the following group are used: **acetaminophen** (**paracetamol**), acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β-carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dicoumarol, digitoxin,. .
.

L117 ANSWER 10 OF 10 USPATFULL on STN
AN 89:7424 USPATFULL
TI Sustained release pharmaceutical plaster
IN Hidaka, Osafumi, Tokyo, Japan
Sakai, Tomoki, Tokyo, Japan
Sakano, Toyoaki, Tokyo, Japan
PA Teijin Limited, Osaka, Japan (non-U.S. corporation)
PI US 4801458 19890131 <--
WO 8700046 19870115 <--
AI US 1987-17946 19870224 (7) <--
WO 1986-JP317 19860623 <--
19870224 PCT 371 date
19870224 PCT 102(e) date
PRAI JP 1985-135917 19850624 <--
DT Utility
FS Granted
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Horne, L. R.
LREP Sughrue, Mion, Zinn, Macpeak & Seas
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1055
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A sustained release pharmaceutical plaster which is characterized in that it is a pharmaceutical preparation mainly composed of an adhesive compound layer and a supporter which supports the adhesive compound layer, inside of which there is an arrangement of hollow fibers, that have radially arranged open pores, with their tubular hollows filled with medicines.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 4801458 19890131 <--
WO 8700046 19870115 <--
AI US 1987-17946 19870224 (7) <--
WO 1986-JP317 19860623 <--
19870224 PCT 371 date
19870224 PCT 102(e) date
PRAI JP 1985-135917 19850624 <--
DETD . . . salicylamide, glycol salicylate,l-menthol, aminopyrine, antipyrine, clofezone, ketophenylbutazone, camphor, mentha oil, thymol, isopropylantipyrine, phenylbutazone, feprazone, bezyl nicotimate ester, capsicum extract, capsaicin, **acetaminophen**, oxyphenbutazone, pentazocine, eptazocine, diffunisal, phenazole, mepirizole, piroxicam, benzydamine, phenacetin, tiaramide, bufexamac, flufenamic acid, aluminum flufenamate, indometacin, **tramadol** hydrochloride, ibuprofen, acemetacin, sulpyrine, guaiazulene, ketoprofen, flurbiprofen, diclofenac sodium, fenoprofen, naproxen, clidanac, sulindac, benoxabrofen, indoprofen, mefenamic acid, tolmetin, metiazinic acid,. . .

=> => fil biosis
FILE 'BIOSIS' ENTERED AT 08:53:01 ON 06 APR 2005
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 1 April 2005 (20050401/ED)

FILE RELOADED: 19 October 2003.

=> d l167 all tot

L167 ANSWER 1 OF 2 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN **1991:353490** BIOSIS
DN **PREV199141038005; BR41:38005**
TI ANALGESIC ORAL EFFICACY OF **TRAMADOL** HYDROCHLORIDE IN PAIN FOLLOWING CESAREAN SECTION.
AU SUNSHINE A [Reprint author]; ZIGHELBOIM I; OLSON N Z; DECASTRO A; MINN F L
CS NYU MED CENT, NEW YORK, NY, USA
SO Clinical Pharmacology and Therapeutics, (1991) Vol. 49, No. 2, pp. 181.
Meeting Info.: NINETY-SECOND ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CLINICAL PHARMACOLOGY AND THERAPEUTICS, SAN ANTONIO, TEXAS, USA, MARCH 13-15, 1991. CLIN PHARMACOL THER.
CODEN: CLPTAT. ISSN: 0009-9236.
DT Conference; (Meeting)
FS BR
LA ENGLISH
ED Entered STN: 1 Aug 1991
Last Updated on STN: 11 Sep 1991
CC General biology - Symposia, transactions and proc
Biochemistry studies - General 10060
Anatomy and Histology - Surgery 11105
Pathology - Therapy 12512
Reproductive system - General and methods 16501
Nervous system - Pathology 20506
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Clinical pharmacology 22005
Pharmacology - Neuropharmacology 22024
Toxicology - Pharmacology 22504
IT Major Concepts

No Abstracts - Relevance depends on full-text Publication

Nervous System (Neural Coordination); Pharmacology; Reproductive System (Reproduction); Surgery (Medical Sciences)
IT Miscellaneous Descriptors
ABSTRACT HUMAN **ACETAMINOPHEN** ANALGESIC-DRUG NO ADVERSE EFFECTS PHARMACOKINETICS
RN **36282-47-0** (**TRAMADOL** HYDROCHLORIDE)
103-90-2 (**ACETAMINOPHEN**)

L167 ANSWER 2 OF 2 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN **1986:247721** BIOSIS
DN **PREV198631002433; BR31:2433**
TI ANALGESICS IN DENTAL PRACTICE.
AU HOTZ G [Reprint author]
CS ABTEILUNG FUER ZAHNAERZTLICHE-UND KIEFERCHIRURGIE, ZZMK, HOSPITALSTRASSE 1, D-6900 HEIDELBERG 1
SO ZWR (Heidelberg), (1985) Vol. 94, No. 11, pp. 892-896.
CODEN: ZWRSBR. ISSN: 0044-166X.
DT Article
FS BR
LA GERMAN
ED Entered STN: 13 Jun 1986
Last Updated on STN: 13 Jun 1986
CC Biochemistry studies - General 10060
Pathology - Therapy 12512
Dental biology - General and methods 19001
Pharmacology - Clinical pharmacology 22005
Pharmacology - Neuropharmacology 22024
IT Major Concepts
Dental and Oral System (Ingestion and Assimilation); Pharmacology
IT Miscellaneous Descriptors
HUMAN **PARACETAMOL** PHENACETIN PROPYPHENAZONE CAFFEINE CODEIN PHOSPHATE BUTALBITAL SALICYLAMIDE BUPRENORPHINE DEXTROMORAMIDE HYDROMORPHONE LEVO METHADONE MORPHINE PENTAZOCINE **PARACETAMOL** PETHIDINE PIRITRAMIDE CODEINE DIHYDROCODEINE DEXTROPROPOXYPHENE NEFOPAM NALOXONE TILIDINE **TRAMADOL** ANALGESIC-DRUG
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN **103-90-2** (**PARACETAMOL**)
62-44-2 (PHENACETIN)
58-08-2 (CAFFEINE)
14265-44-2 (PHOSPHATE)
77-26-9 (BUTALBITAL)
65-45-2 (SALICYLAMIDE)
52485-79-7 (BUPRENORPHINE)
357-56-2 (DEXTROMORAMIDE)
466-99-9 (HYDROMORPHONE)
125-58-6 (LEVO-METHADONE)
57-27-2 (MORPHINE)
359-83-1 (PENTAZOCINE)
57-42-1 (PETHIDINE)
302-41-0 (PIRITRAMIDE)
76-57-3 (CODEINE)
125-28-0 (DIHYDROCODEINE)
469-62-5 (DEXTROPROPOXYPHENE)
13669-70-0 (NEFOPAM)
465-65-6 (NALOXONE)
51931-66-9 (TILIDINE)
27203-92-5 (**TRAMADOL**)
20380-58-9 (TILIDINE)

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=> d his

     (FILE 'HOME' ENTERED AT 07:06:24 ON 06 APR 2005)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 07:06:33 ON 06 APR 2005
               E TRAMADOL/CN
L1             1 S E3
               E C16H25NO2/MF
L2           149 S E3 AND (46.150.18 AND 46.150.1)/RID
L3             4 S L2 AND TRAMADOL
L4            29 S L2 AND CYCLOHEXANOL AND DIMETHYLAMINO AND METHOXYPHENYL
L5            25 S L4 NOT L1,L3
L6            13 S L5 AND 3 METHOXYPHENYL
               SEL RN 4 5 13
L7             3 S E1-E3
L8             7 S L1,L3,L7
               SEL RN
L9            71 S E4-E10/CRN
               E ACETAMINOPHEN/CN
L10            1 S E3
L11          395 S C8H9NO2/MF AND 46.150.18/RID AND 1/NR
L12           66 S L11 AND HYDROXYPHENYL
L13           36 S L12 AND ACETAMIDE
L14           24 S L13 AND 4
L15            1 S L10 AND L14
               SEL RN
L16          325 S E1/CRN
L17            2 S L9 AND L16
L18           69 S L9 NOT L17
L19           43 S L18 AND (MXS/CI OR COMPD OR WITH)
L20           26 S L18 NOT L19
L21          301 S L16 AND (MXS/CI OR COMPD OR WITH)
L22            2 S L21 AND C16H25NO2
L23            2 S L17,L22
L24           24 S L16 NOT L21

     FILE 'HCAPLUS' ENTERED AT 07:23:11 ON 06 APR 2005
L25           15 S L23
L26            2 S L25 AND (RAFFA R? OR VAUGHT J?)/AU
L27            1 S L25 AND (ORTHO? OR MCNEIL? OR MC NEIL?)/PA,CS
L28            1 S L25 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L29            2 S L26-L28
L30         1058 S L8 OR L20
L31         1144 S TRAMADOL OR U26255A OR U()(26255A OR 26255 A OR 26 255A OR 26
L32           17 S 2 DIMETHYLAMINO METHYL 1 3 METHOXYPHENYL CYCLOHEXANOL
L33            1 S 2()(DIMETHYL OR DIMETHYL OR DI METHYL OR DIME)()AMINO METHYL
L34           45 S TRAMAL OR CG315 OR CG 315
L35         1198 S L30-L34
L36        11440 S L15 OR L24
L37         7018 S ACETAMINOPHEN? OR TYLENOL
L38           98 S (4 OR P OR PARA)()(HYDROXYPHENYL OR HYDROXY PHENYL)()ACETAMID
L39         4876 S PARACETAMOL
L40           15 S 4()(ACETYLAMINO OR ACETYL AMINO)()PHENOL
L41          463 S (4 OR P)()ACETAMIDOPHENOL
L42          404 S (4 OR P)()(HYDROXYACETANILIDE OR HYDROXY ACETANILIDE)
L43           63 S ABENSANIL OR ACAMOL OR ACENOL OR ACETAGESIC OR ACETALGIN OR A
L44          368 S CLARATAL OR CLIXODYNE OR CROCIN# OR DAFALGAN# OR DAPHALGAN# O
L45          175 S FEBROGESIC OR FEBRO GESIC OR FEBROLIN# OR FENDON# OR FEPANIL#
L46         4951 S NEBS OR NOBEDON# OR NSC109028 OR NSC()(109028 OR 109 028) OR
L47          990 S PARALEN# OR PARAMOL? OR PARASPEN# OR PARELAN# OR PARMOL OR PA
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L48           8 S TABALGIN# OR TACHIPIRINA OR TAPAR OR TEMLO OR TEMPANAL OR TEM
L49          11 S ACETYL(1W)(HYDROXYANILINE OR HYDROXY ANILINE)
L50         327 S ACETYLAMINOPHENOL OR ACETYL AMINOPHENOL OR ACETYL AMINO PHENO
L51        1563 S ACETANILIDE(L)HYDROXY
L52         372 S ACETYL(1W)(AMINOPHENOL OR AMINO PHENOL)
L53       16899 S L36-L52
L54         201 S L35 AND L53
L55           6 S L54 AND (RAFFA ? OR VAUGHT ?)/AU
L56           5 S L54 AND (ORTHO? OR MCNEIL? OR MC NEIL?)/PA,CS
L57           9 S L55,L56
L58           8 S L57 NOT PSOAS/TI
L59          12 S L54 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L60          10 S L59 NOT L29,L58
                SEL DN AN 1 2
L61           2 S L60 AND E2-E7
L62          10 S L29,L58,L61
L63          10 S L62 AND L25-L62
L64           4 S L63 AND TRAMADOL(S)(HCL OR HYDROCHLORIDE)
L65          10 S L63,L64
                SEL RN

     FILE 'REGISTRY' ENTERED AT 07:51:18 ON 06 APR 2005
L66         192 S E8-E199
L67           2 S L66 AND L23
L68           6 S L66 AND L8,L9
L69          17 S L66 AND L15,L16
L70          10 S L66 AND L24
L71           6 S L69 NOT L15,L70
L72           5 S L71 NOT 330988-71-1
L73          19 S L67,L68,L70,L72
L74         173 S L66 NOT L73
L75           8 S L74 AND (46.150.18 AND 46.150.1)/RID
                SEL RN 2-6
L76           5 S E200-E204
L77          24 S L73,L76

     FILE 'HCAPLUS' ENTERED AT 07:57:05 ON 06 APR 2005
L78          10 S L77 AND L65
L79          94 S L76
L80        1124 S ?TRAMADOL?
L81         194 S L79,L80 AND L53
L82          10 S L81 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L83           6 S L82 NOT L78
L84          10 S L78 AND L25-L65,L78-L83
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 07:58:51 ON 06 APR 2005
L85          25 S E205-E229

     FILE 'REGISTRY' ENTERED AT 07:59:12 ON 06 APR 2005
L86           6 S L8 NOT L85

     FILE 'HCAPLUS' ENTERED AT 08:00:31 ON 06 APR 2005

     FILE 'WPIX' ENTERED AT 08:03:06 ON 06 APR 2005
L87         335 S L31/BIX OR L32/BIX OR L33/BIX OR L34/BIX
                E TRAMADOL/DCN
                E E3+ALL
L88         267 S E2
                E TRAMADOL/CN
L89           7 S E4-E13
L90          50 S (RAF613 OR RA4BD7 OR RA0HAR OR RAOHAR OR RA0HAF OR RAOHAF OR
L91         364 S L87,L88,L90
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L92         2169 S L37/BIX OR L38/BIX OR L39/BIX OR L40/BIX OR L41/BIX OR L42/BI
                 E ACETAMINOPHEN/DCN
                 E E3+ALL
L93         1338 S E2 OR 0758/DRN
L94          646 S E4
                 E ACETAMINOPHEN/CN
L95         2587 S L92-L94
L96           71 S L91 AND L95
L97            3 S L96 AND (RAFFA ? OR VAUGHT ?)/AU
L98            4 S L96 AND (MCNEIL? OR MC NEIL? OR ORTHO?)/PA,CS
L99            4 S L97,L98
                 E 9312-29401/DCN
L100           1 S E3,E4
L101           4 S L99,L100
L102          67 S L96 NOT L101
L103           0 S L102 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L104        3279 S L95 OR A61K031-167/IPC
L105          75 S L104 AND L91
L106           4 S L105 NOT L96
L107           4 S L101 AND L87-L106

     FILE 'WPIX' ENTERED AT 08:21:24 ON 06 APR 2005

     FILE 'USPATFULL' ENTERED AT 08:21:55 ON 06 APR 2005
L108        1267 S L35
L109       12423 S L53
L110           0 S L23
L111         562 S L108 AND L109
L112           6 S L111 AND (RAFFA ? OR VAUGHT ?)/AU
L113           6 S L85 AND L112
L114         151 S L85 AND L111
L115         556 S L111,L114 NOT L113
L116           4 S L115 AND (PY<=1991 OR PRY<=1991 OR AY<=1991)
L117          10 S L113,L116 AND L108-L116

     FILE 'USPATFULL' ENTERED AT 08:26:20 ON 06 APR 2005

     FILE 'DRUGU' ENTERED AT 08:27:30 ON 06 APR 2005
L118        1229 S L31-L34
L119       14638 S L37-L52
L120         318 S L118 AND L119
L121          44 S L120 AND PY<=1991

     FILE 'PS' ENTERED AT 08:34:43 ON 06 APR 2005
L122           1 S L31-L34 OR ?TRAMADOL?

     FILE 'DDFB' ENTERED AT 08:35:59 ON 06 APR 2005
L123          52 S L31-L34
L124        3497 S L37-L52
L125           4 S L123 AND L124

     FILE 'EMBASE' ENTERED AT 08:38:10 ON 06 APR 2005
L126        3560 S L31-L34 OR ?TRAMADOL?
L127           0 S L23
L128        3519 S L8 OR L20
L129        3560 S L126,L128
L130       30205 S L37-L52
L131       28444 S L15 OR L24
L132       30205 S L130,L131
L133        1118 S L129 AND L132
L134          58 S L133 AND PY<=1991
L135         456 S (TRAMADOL(L)CB)/CT
L136        2569 S (PARACETAMOL(L)CB)/CT
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L137          1 S L134 AND L135
L138          0 S L134 AND L136
L139         57 S L134 NOT L137
L140         47 S L139 NOT AB/FA
L141         10 S L139 NOT L140
L142          0 S L140 AND SYNERG?

     FILE 'CANCERLIT' ENTERED AT 08:44:22 ON 06 APR 2005
L143          0 S L23
L144         43 S L8 OR L20
L145         55 S L31-L34 OR ?TRAMADOL?
L146         55 S L144,L145
L147        430 S L15 OR L24
L148        863 S L37-L52
L149        863 S L147,L148
L150          4 S L146 AND L149

     FILE 'MEDLINE' ENTERED AT 08:45:51 ON 06 APR 2005
L151          0 S L23
L152        874 S L8 OR L20
L153       1128 S L31-L34 OR ?TRAMADOL?
L154       1128 S L152,L153
L155       8849 S L15 OR L24
L156      11998 S L37-L52
L157      11998 S L155,L156
L158        136 S L154 AND L157
L159          1 S L158 AND PY<=1991

     FILE 'BIOSIS' ENTERED AT 08:47:59 ON 06 APR 2005
                E RAFFA R/AU
L160        179 S E3,E5,E7,E9
                E VAUGHT J/AU
L161        173 S E3,E7,E9-E13
L162          0 S L23
L163       1095 S L8 OR L20 OR L31-L34 OR ?TRAMADOL?
L164      11900 S L15 OR L24 OR L37-L52
L165         98 S L163 AND L164
L166          5 S L165 AND PY<=1991
                SEL DN AN 1 5
L167          2 S L166 AND E1-E6
L168         31 S L160,L161 AND L163,L164
L169          3 S L168 AND L165
L170         28 S L168 NOT L169

     FILE 'BIOSIS' ENTERED AT 08:53:01 ON 06 APR 2005

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